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DR. FRANK C. BRESSLER

BULLETIN

OF THE

SCHOOL OF MEDICINE

UNIVERSITY OF MARYLAND

Vol. 25 JULY, 1940 No. 1

EDITORIAL

Dedication of the Frank C. Bressler Research Laboratory of the School of Medicine, University of Maryland

On May 30, 1940 the Frank C. Bressler Research Laboratory was formally dedicated. The building has been occupied since January 1, 1940 by some of the preclinical departments. On the occasion of the dedication, research activity was in evidence in all departments and the commodious teaching facilities were open for inspection. During the morning many of the alumni and friends of the University visited the various departments and displayed intense interest in the research projects in progress in the departments occupying the Bressler Building.

A luncheon was held in the University Hospital just prior to the formal dedication, and was attended by a large and enthusiastic group of alumni. At 2:30 P.M., Emeritus Dean J. M. H. Rowland convoked the formal dedicatory ceremonies in the old Westminster Presbyterian Church. President H. C. Byrd of the University of Maryland welcomed the visiting delegates and friends and commented on the achievements and magnanimity of Dr. Bressler. On behalf of the Board of Regents of the University, Dr. Byrd accepted the key of the building from Mr. Howard G. Hall, representing Crisp and Edmunds, the architects of the building.

Mr. Harry A. Kohlerman, cotrustee of the Bressler estate and lifelong friend of Dr. Bressler, gave a sincere and inspiring appreciation of the donor during which the spirit of the benefactor pervaded the audience. Mr. Kohlerman's remarks are included in this issue of the *Bulletin.*

Dr. Carl Voegtlin, Chief of the National Cancer Institute of the United States Public Health Service, delivered the dedicatory address.

Dr. Voegtlin is a graduate of the University of Freiburg and has engaged in many phases of research in the medical sciences extending over a quarter of a century in this country. His address, which is published in this issue of the *Bulletin*, was instructive and inspirational.

The benediction was pronounced by the Rev. Bruce H. MacDonald of the Westminster Presbyterian Church. Following the exercises, many of the alumni and their friends visited the laboratories of the Bressler Building. The medical alumni banquet was held at the Lord Baltimore Hotel the same evening.

John C. Krantz, Jr.,
Chairman, Dedication Committee.

PROGRAM OF THE DEDICATION OF THE FRANK C. BRESSLER RESEARCH LABORATORY

Thursday, May 30, 1940

2:30 P.M.

Westminster Presbyterian Church

Fayette and Greene Streets

Processional—*Presiding Officer*—Dr. J. M. H. Rowland, Dean Emeritus, School of Medicine.
Invocation—Rev. Bruce H. McDonald, Pastor Westminster Presbyterian Church.
Greetings to Visiting Delegates—Dr. H. Clifton Byrd, President of the University.
Presentation of Key of Bressler Building—By Mr. Howard G. Hall, Representing Crisp & Edmunds, Architects.
An Appreciation of Dr. Frank C. Bressler—By Mr. Harry A. Kohlerman.
Address—Dr. Carl Voegtlin, Chief, National Cancer Institute, United States Public Health Service.
Benediction—Rev. Bruce H. McDonald.
Recessional—
Inspection of Bressler Building.

AN APPRECIATION OF DR. FRANK C. BRESSLER*

HARRY A. KOHLERMAN, LL.B.

BALTIMORE, MD.

With those who had the privilege of frequent association with Dr. Frank C. Bressler there will ever abide the precious memory, not only of the work of an able doctor, but of companionship with a beautiful spirit, and an extraordinary combination of grace and power.

Dr. Bressler, who had risen from the ranks to the medical profession, was born in New York City in 1855. His father, Frank Bressler, was born in Frankenthal, Bavaria, came to America and settled in New York, where he engaged in business until the Civil War, when he joined the Fifty-fifth New York Zouaves. At the close of the war he returned to New York and after a few years went abroad to superintend the education of his son, Frank C. Bressler, at Frankenthal, Bavaria. After three years in Bavaria they returned to New York. Later the family moved to Pittsburgh and then to Wilkes Barre, Pennsylvania, where young Frank C. Bressler attended the public schools, after which he pursued a course in classical study under private instruction by an eminent member of the Wilkes Barre bar. He completed a general course in the State Normal School of Millersville, Pennsylvania, and then took up the study of medicine under Dr. Spare of Luzerne County, Pennsylvania.

In 1883 he matriculated at the College of Physicians and Surgeons of Baltimore, Maryland, and at the same time entered the office of Doctor J. W. Chambers as a private pupil. In 1885 he received the degree of doctor of medicine with honor. Several years after graduation he was appointed clinical professor of children's diseases in the College of Physicians and Surgeons.

Dr. Bressler was a member of the Medical and Chirurgical Faculty of Maryland and president of the Baltimore Medical and Surgical Society. For a number of years he served as surgeon at the Hebrew Hospital, now Sinai Hospital, and as local surgeon to the Pennsylvania Railroad Company.

He was exceptionally kind and considerate to his patients, and his presence created a feeling of confidence and security. It was always his pleasure to help others.

Recently a patient of Dr. Bressler, a man of modest means, told of the doctor treating one of his four children, after which he paid his bill amounting to $27.00. Dr. Bressler knew that this man's home was mortgaged so he returned the money and told his patient to pay the $27.00 on his mortgage account.

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* Address at the dedication of the Frank C. Bressler Research Laboratory, May 30, 1940.

A few years after Dr. Bressler began to practice medicine he married Miss Emma Gehring, the daughter of George Gehring, a prominent jeweler of Baltimore. They had one child, Gertrude, who married Calvert Steuart. Mrs. Bressler died on March 17, 1930 and his daughter, Gertrude Bressler Steuart, died on September 8, 1934, nine months before the death of Dr. Bressler.

While the practice of medicine was the main occupation of his life, Dr. Bressler found time to be interested in many other things. He traveled extensively, through North America, Europe, Asia and Africa. It was interesting to hear him speak of his travels. Dr. Bressler was well read, fond of music, and he enjoyed fishing. He took an interest in civic affairs and was appointed a member of the School Board of Baltimore City by Mayor Hooper, and served on this Board with the late D. C. Gilman, former president of the Johns Hopkins University.

All his life he was devoted to charity. At the time of his death he was president of the Baltimore Eastern Dispensary and president of the John Frederick Wiessner Orphan Asylum, and rarely missed a meeting at either of these societies. He also attended the children at the General Orphan Home at Catonsville.

It is well known that he was deeply interested in the children at the John Frederick Wiessner Orphan Asylum, that he frequently visited them, and contributed liberally to their support and maintenance.

Kind, genial and considerate, he bound those with whom he came in contact to him with chains of affection, which neither time nor death can sever. Generosity, honesty and humanity were the outstanding traits of his character. He loved his profession, he loved the orphans, he loved his fellowmen. He was interested in their sorrows and in their joys.

And so, on May 18, 1935, when the final summons came, loved and honored by his fellowmen, in his cherished home in this community, where he spent so many years of his life, he gave his soul to his God, under whose colors he had fought; he gave his body to the earth of the State of Maryland, which he loved; and he gave his worldly goods to the great University of Maryland, for a research laboratory, for the betterment of humanity.

THE APPROACHES TO CANCER RESEARCH*

CARL VOEGTLIN, Ph.D.†

BETHESDA, MD.

I fully appreciate the honor of your invitation to address you on this memorable occasion. Coming here today for me is like coming home, since I spent over seven years of my life, from 1905 to 1913, in Baltimore on the faculty of your sister medical school—Johns Hopkins. It was then that I first met your distinguished alumnus, Dr. J. Whitridge Williams. Later on I became acquainted with members of your present faculty—Dr. J. C. Krantz, Jr., Dr. M. C. Pincoffs and Dr. E. Uhlenhuth.

To your Medical School and the building committee I extend congratulations for these excellent laboratories. I am sure that you who are working in these new quarters will live up to the fine old traditions of your institution.

Dr. Krantz has requested me to speak on some phases of medical research. As I have been interested for many years in the cancer problem, I have chosen this as my topic.

It is a readily understandable fact that progress in research resulting in a better control of certain diseases unavoidably leads to a shift in the relative position of these diseases as causes of death.

This has been strikingly reflected in the cancer mortality during the present century. The elimination of typhoid fever by sanitation, and the remarkable and continuous decreases in the mortality from tuberculosis, digestive diseases of infants, nutritional and other diseases have greatly increased the average longevity. For this reason and because cancer, as a rule, requires many years for its development, cancer today is next to heart disease as a major cause of death. Cancer has moved from ninth place in 1900 to second place in 1940.

In 1938 there were recorded in the United States 149,000 deaths from cancer. It is estimated that the ideal application of all existing knowledge of cancer control would have saved about 25 per cent, or 35,000 lives, leaving nearly 115,000 persons doomed to die. Unless prevailing conditions are radically improved the outlook for the future is even worse, with an estimated total yearly cancer mortality ten years from now of close to 200,000. Similar statistical data are available from other countries.

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* Address made at the dedication of the Frank C. Bressler Research Laboratory of the School of Medicine, University of Maryland, May 30, 1940.

† Chief, National Cancer Institute, National Institute of Health, United States Public Health Service.

What can be done in order to improve this serious situation, apart from the application of recognized control measures? There is only one answer: the acquisition of new knowledge through research. Until recent years cancer research, strange as it may seem, has been a much-neglected field. Fortunately, there has come the realization that the conquest of cancer, as that of other diseases, must come about through scientific investigation.

Cancer is a unique disease. It is not contagious, and there is every reason to believe that it is *not* caused by a specific infectious agent. Clinical experience and particularly animal experimentation have clearly shown that cancers are the result of the transformation of normal body cells into malignant cells. The characteristic biological behavior of cancerous tissues must be attributed, therefore, to these permanently altered cells. Cancer cells are endowed with an abnormally high rate of multiplication, as compared with most normal cells. They have the power of invading and destroying normal tissues, thus causing death.

Therefore, the fundamental problem in cancer is to find a satisfactory answer to two questions: (1) the causes for the transformation of normal cells into cancer cells; and (2) the reasons why cancer cells differ from normal cells.

In many respects cancer is not a single disease but rather a group of diseases, each type of cancer being derived from a different type of normal cell, and each having its peculiar characteristics.

CAUSATIVE FACTORS

To a great extent, because of experimental research the view is rapidly gaining ground that the different types of cancer are caused by many and diverse factors. These may be divided into two broad groups: (1) so-called *external* or extrinsic causative factors; and (2) *internal* or intrinsic causative factors. The former act from without, the latter from within the animal body.

The following are examples of *external causative factors:*

A. Excessive exposure to roentgen rays and radioactive material extending over many years as causes of skin cancer and leukemia in certain occupations.

B. Excessive exposure to strong sunlight (and possibly other atmospheric conditions, i.e., heat, dust) as the cause of skin cancer in sailors and farmers.

C. Certain chemicals used in the manufacture of aniline dyes as causes of cancer of the urinary bladder in factory workers.

D. Soot and certain coal tars as causes of skin cancer in chimney sweeps and workers handling coal tar.

These so-called *occupational* cancers can be prevented by controlling the respective causative external factors, for instance, by effective protection against radiations, by improvements in manufacturing technique of coal tar products, etc.

The discovery of some of these external causative factors has opened up a most important field for experimental research and has led to the following:

I. The isolation from certain coal tars of a pure and powerful cancer-producing chemical—3,4 benzpyrine.

II. The chemical synthesis of a very large number of cancer-producing chemicals.

III. The production of cancers in different organs of animals by means of these chemicals. These cancers have the same characteristics as the cancers in the same tissues of humans.

IV. The possibility of studying the manner whereby these chemicals produce malignant cells.

V. The opportunity of defining more precisely the rather vague term *chronic irritation* of tissues, which for a long time has been regarded as a likely cancer-producing factor.

I believe that the search for additional external factors has by no means been exhausted. In this connection there is an urgent need for epidemiological and experimental investigations. Careful studies of the precancerous histories of cancer patients, with emphasis on environmental conditions and mode of living, may well reveal interesting and important information. There are various reasons why such work has been neglected. One of these is the pressure put on the cancer specialist by the never-ending urgent need of diagnosing and treating the large number of patients, leaving little if any time for etiological research. It would seem that progress in this difficult field can only be made by full-time investigators having the necessary training and inquisitive mentality.

The laboratory investigator also has an opportunity to make his contribution. To mention only two illustrations, he can study on animals the possible relation of atmospheric dust and tobacco smoking to cancer of the lung, or the possible relation of abnormalities in diet to stomach cancer. Cancer of the lung appears to be increasing, and stomach cancer, owing to great difficulties in early diagnosis, accounts for a high percentage of the total cancer mortality. Such work promises to yield important knowledge for the prevention of certain kinds of cancer, just as the discovery of external factors for the above-mentioned occupational cancers has furnished practical preventive measures.

Evidence is also rapidly accumulating which indicates that cancer is partly the result of *internal factors*. Experiments with animals have shown clearly that abnormalities in the production of certain hormones, especially the sex hormones, are in part responsible for cancer of the breast, the uterus, and the testicle of animals. This promising and complex field is being actively investigated, and much important knowledge will undoubtedly be gained by further systematic work. Suffice it to mention that estrone, one of the hormones of the ovary, is known to produce breast cancer under certain conditions in female as well as male mice.

Now it is evident from the chemical structure of this hormone that it belongs to a very important group of chemicals which occur in the animal body—the steroids. It is of great interest, therefore, to prepare and to test for their cancer-producing properties chemicals belonging to this class, in the hope of discovering compounds which are produced in the body as a result of an abnormal steroid metabolism. The aim is to explain the causation of some of the so-called spontaneous animal and human cancers. This is only one of many striking examples of the part played by chemistry in cancer research.

There are still other internal causative factors. Work with highly inbred strains of mice has shown clearly that heredity plays an important part. We have strains of mice with a very high or very low incidence of breast cancer. Other strains develop at an advanced age a high percentage of lung or liver cancers. There are some indications that hereditary constitution may also play a minor role in human cancer, though it is well to point out that human beings obviously are not inbred.

The principal value of inbred strains of animals is that the hereditary factors can be controlled, thus permitting the study of other causative factors. For instance, it has been shown with eight highly inbred strains of mice that they varied in their susceptibility not only to spontaneous breast and lung tumors, but also to chemically-induced subcutaneous and lung tumors. None of them was susceptible or resistant to cancer in general. This is further convincing proof that cancer is a group of diseases and not a single disease.

BIOLOGY OF CANCER CELLS

This leads us to the most fundamental part of the whole cancer problem—the biology of cancer cells. Normal as well as cancer cells are by far the most complex physical and chemical organizations known. Our present concept of the physical structure and especially of the chemistry of these cells is very crude indeed. Nevertheless, progress is being made by means of improved technical methods. We know, of course, that the principal parts of cells are the nucleus and the surrounding cytoplasm. For many years investigators have tried to explain the characteristic behavior of cancer cells on the assumption of an abnormality of the minute components of chromosomes, i.e., genes, of the cell nucleus. Some support for this assumption has come from the above-mentioned experiments on hereditary factors. However, until we have more conclusive evidence, it is better toleave this question open and to consider that either nucleus or cytoplasm, or both, undergo a specific change. The possibility that this change may be connected with a specific change of a specific cell protein deserves serious consideration in view of the theoretically unlimited variability in protein structure. This problem, which covers an almost virgin field, is now being attacked.

A vast field has recently been opened up by the discovery of radioactive and nonradioactive isotopes of the chemical elements, which will serve as an entirely new approach to the study of the metabolism of cancer cells and its relation to the metabolism of the body as a whole. By incorporating these isotopes into the molecular structure of natural organic compound (amino acids, sugars, etc.), it will be feasible to trace these compounds and their conversion products in their course through the body. By this technique information will be secured concerning the synthesis of the organic constituents of cancer cells and normal cells, data which will be of good significance for an understanding of the characteristic growth of cancerous tissues. This shows how modern physics contributes to cancer research.

There are indications that the high fermentation of certain sugars by cancerous tissue plays a role in the destructive action of cancer cells on the surrounding normal cells.

Restriction in the diet of certain amino acids, which are the essential building stones of body proteins and the growth of tissues, causes a striking inhibition of the growth of breast cancer in mice, without apparently interfering with the well-being of the animals. This is of considerable theoretical interest.

Interesting studies are also in progress with tissue enzymes, those important regulators of chemical reactions in cells.

DIAGNOSTIC TESTS FOR CANCER

A most important line of investigation is the search for tests for the early diagnosis of internal cancers. The curability of these cancers depends on early recognition, before the malignant growth has spread from the original site to more distant parts of the body. The reason why so many lives are lost from cancer of the stomach, liver and lung, to mention only a few types, is because the early stages of these diseases cannot be recognized except in a small percentage of cases. Tests based on the activity of enzymes in blood serum have either been not specific enough for cancer or they have yielded good results only in the more advanced stage, when a diagnosis can be made by other means. It is very urgent, therefore, to continue the search for more sensitive and specific tests.

TREATMENT OF CANCER

As first stated, cancer can be cured only if localized. The reason for this is that surgery, roentgen rays, and radium are measures which only can be applied for the complete destruction of localized cancerous growth. While improvements may come from the use of supervoltage roentgen rays and neutrons alone, these powerful radiations have the inherent effect of not only destroying cancer cells but many normal cells as well. In other words, it does not seem at this time that these high-energy radiations could be applied safely in order to cause the destruction not only of the primary, but also of the secondary growths of the more advanced stage of cancer. In this connection we have very recent information showing that the serious hazards incident to exposure of professional personnel to high-energy radiations are by no means fully appreciated. Much work is needed to study the remote action of these radiations in order to safeguard the welfare of physicists and other personnel in cancer clinics. The increasing use of roentgen rays in industry presents another problem.

A different approach is to discover chemicals with a *specific* action on cancer cells. Much experimental work has been done and is in progress. The proposition is an extremely difficult one, but who could have foreseen only a few years ago the remarkable results now obtained with the sulfanilamide type of drugs in the treatment of many serious diseases? For the present and until we have a clearer conception of the cancer cell, efforts in this direction will have to be confined to empirical testing of compounds, as was the case in the initial work which led to the discovery of the arsphenamines and sulfanilamide. However, in view of what has been said concerning the diversity of cancers, it is unlikely that a curative chemical agent for all forms of cancer will ever be found. An experimental study of the action of certain bacterial filtrates on cancers of connective tissue origin is in progress.

ORGANIZATION OF CANCER RESEARCH

In this brief time it was possible only to sketch some of the approaches of cancer research. Before closing may I be permitted to make some remarks on the ways and means of carrying out such plans? Cancer research is in many respects unique because of the broad scope and the diversity of the problems. The individual scientist, whether biophysicist, chemist, pathologist, and so forth, can never hope to follow through his own problem, because sooner or later he will require the collaboration and criticism of scientists with other training. Cancer research requires team work. Any major cancer research organization should be knit together closely, without however interfering with that most valuable asset—individual imagination and initiative.

The individual worker must be prepared to be interested primarily in the application of his special knowledge to a particular phase of cancer research. In addition he has to acquire, through intimate contact with other specialists, a fairly general view of the cancer problem. Cancer research is a life job and demands unusual courage, imagination, objectivity and perseverance. Long range and coordinated planning is essential.

Such were the ideas in organizing the National Cancer Institute. In its short existence this plan has already proved its value.

In conclusion, I want to emphasize the need for collaboration in all medical research in order to counteract the undesirable effects of overspecialization. In your splendid new building you not only will have physical contact, but I hope a maximum of close intellectual relationship. May you keep high the torch of true knowledge in this war-torn world.

A SYNOPSIS OF SULFAPYRIDINE*

CHRISTOPHER C. SHAW, M.D.

BELLOWS FALLS, VERMONT

The advent of the sulfonamide derivatives in the past five years has revolutionized the chemotherapy of bacterial infections. The first of these compounds was sulfanilamide or prontylin and its derivatives, notably prontosil, neoprontosil, septazine, disulon, uliron, and sulfapyridine. Other related chemical formulas are being put to pharmacological and clinical trial and the whole field of chemotherapy has entered on a new phase of development. A product termed sulfamethylthiazol (1) has given encouraging results in the control of infections resulting from the staphylococcus aureus and is proving to be less toxic and more efficacious than sulfapyridine. As time goes on, further progress in chemotherapy may be anticipated and the study of this field will become increasingly more complex. It is therefore appropriate to take stock occasionally of the situation and to review the progress in a given sector with the idea of familiarizing one's self with the knowledge at hand.

For the past two years, sulfapyridine has been available for study and during the year ending March 12, 1940 has been distributed to the general medical public for widespread trial (and error). Sulfapyridine is a potent drug and worthy of special care and consideration. A brief synopsis of this compound dealing with its chemotherapeutic action, its toxic aspects and its clinical applications may be desirable at this time.

Sulfapyridine was first synthesized by Ewins in England and independently by Northey in the United States as 2(para-aminobenzenesulfonamido) pyridine (2). The product was called "Dagenan" or M. & B. 693 by the May & Baker Co., Ltd. In 1938 Whitby (3) of London found sulfapyridine to be five times more effective, weight for weight, than sulfanilamide in the treatment of experimental hemolytic streptococcic infections in mice. Long, Bliss and Feinstone (4) in Baltimore obtained similar therapeutic results with the compounds obtained from Northey and from Ewins, but the Baltimore investigators found the ratio of therapeutic effectiveness between sulfapyridine and sulfanilamide somewhat less than that reported by Whitby. Long and his associates conclude on the basis of their experimental and clinical evidence that sulfapyridine is efficacious in

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* Received for publication March 14, 1940.

the treatment of pneumococcic pneumonia, severe staphylococcic and Friedländer's bacillary infections.

The drug occurs as a white crystalline powder of low solubility and is usually given by mouth in the form of tablets or capsules. The soluble sodium salt of sulfapyridine may be prepared freshly and given with caution intravenously in selected cases. The absorption of sulfapyridine is slower than that of sulfanilamide and varies widely in human patients. Identical doses of sulfapyridine by mouth frequently give very dissimilar blood levels in different persons. Hobson and MacQuaide (5) found that the same individual absorbs sulfapyridine more rapidly in health than when diseased. The low solubility of the drug is probably responsible for its poor absorption. From two to five times as much sulfapyridine must be given by mouth to attain the concentrations of the drug in the blood comparable to those obtained by intravenous injection of the soluble sodium salt. Such a dosage would indicate that an unpredictable amount of the drug must pass unabsorbed through the gastro-intestinal tract when given orally. This should serve to emphasize the importance of frequently determining the concentration of the drug in the blood of every patient receiving sulfapyridine.

The drug is absorbed in the free or nonacetylated form but a variable amount gradually becomes conjugated in the tissues to acetylsulfapyridine, with resulting depletion of the free form. In most patients a parallelism exists between the blood level of the free and conjugated forms of the drug from day to day, but in about one-fifth of the patients an unusually rapid acetylation of sulfapyridine may occur ranging from 60 to 75 per cent of the total drug in the circulation. In such cases an estimation of the free form alone is both unreliable and misleading. It is therefore preferable to make daily determinations of both the free and conjugated sulfapyridine blood levels. Unfortunately, there is as yet no method of determining the rate or degree of acetylation of sulfapyridine in a given patient before administering the drug.

The degree of absorption can be measured by the concentration of sulfapyridine in the blood or by its excretion in the urine. Peak concentrations in the blood occur from four to six hours after the oral administration of a single dose, but this peak level is less than one would expect if a comparable dose of sulfanilamide had been ingested. Moreover, the decline from the sulfapyridine peak level is much slower than that observed following a single dose of sulfanilamide. This is caused, in all probability, by the fact that the urinary excretion of sulfapyridine is much slower and is not complete until three or four days have elapsed after the withdrawal of the drug. Many patients without demonstrable evidence of renal impairment exhibit individual fluctuations in excreting sulfapyridine.

The conjugated or acetylated form of sulfapyridine is both toxic and therapeutically inactive. Acetylsulfapyridine crystals may collect in the renal tubules and pelves and by irritation of the kidney parenchyma produce hematuria. In certain instances this hematuria is associated with increased nitrogen retention, decreased renal function, and anuria. Complete obstruction of the urinary tract by crystalline debris composed chiefly of acetylsulfapyridine has been found at autopsy as the cause of death. The routine administration of bicarbonate of soda together with sulfapyridine will produce an alkaline urine and inhibit in part the precipitation of acetylsulfapyridine. If hematuria develops in spite of this precaution, the drug should be stopped and fluids forced. An extraordinary increase in the highly toxic conjugated fraction has been observed in patients with permanently or temporarily defective renal function. Impairment of the kidneys may occur several days after the sulfapyridine has been discontinued. The first indication of defective renal function is apparent when the twenty-four hour urine volume falls below 1000 cc. The onset of oliguria heralds acute renal insufficiency. If the volume of urine is reduced to 750 cc. in twenty-four hours, disaster lies ahead and can be averted only by interrupting the dosage of sulfapyridine or by terminating it altogether. An accurate measurement of the total urinary output in each twenty-four-hour period of treatment by chemotherapy is therefore of paramount importance.

The toxic manifestations of sulfapyridine therapy include nausea, headache, cyanosis, vomiting and dizziness. Drug fever and morbilliform rashes are frequent. Tingling of the extremities and other symptoms of central nervous system irritation (mental confusion and mild psychosis) may be annoying. Acute hemolytic anemia has been known to occur very rapidly and may necessitate blood transfusions and/or immediate withdrawal of the drug. Agranulocytosis may develop with little, if any, warning and fail to respond to treatment. A fatal outcome as the result of this complication or "accident" occurring during sulfapyridine therapy is not uncommon. In short, the toxic symptoms of sulfapyridine poisoning are essentially those of sulfanilamide poisoning and should be appraised and dealt with in a similar manner. Sulfapyridine, however, is the more toxic and dangerous of the two drugs since it produces greater irritation of the gastrointestinal and urinary tracts.

The nausea and vomiting which accompany ingestion or injection of the drug are the result of central rather than gastric irritation. Demulcents, therefore, will not materially benefit the patient. Fluids should not be forced nor limited to extremes. A fluid intake of 3500 cc. per day is usually adequate. The volume of urinary output is even more significant, as noted above. The diet may be whatever the patient desires. Sulfapyridine is not incompatible with other drugs, which should be administered without hesitancy in conjunction with sulfapyridine when indicated for the welfare and comfort of the patient. The only contraindication for the use of sulfapyridine is a history of previous idiosyncrasy to this drug or to sulfanilamide.

Long (6) states that "in comparison with sulfanilamide the absorption, distribution, conjugation and excretion of sulfapyridine is definitely more irregular and capricious." Rational therapy is therefore more difficult, but the rationale of therapy remains clear.

Sulfapyridine is indicated in the treatment of the pneumococcal pneumonias, whether lobar or lobular in distribution. It is highly efficacious in the treatment of staphylococcal pneumonia and Friedländer bacillary infections. In severe staphylococcal invasions characterized by sepsis, sulfapyridine is one of the most potent weapons known at the present time. In the treatment of gonorrhea, sulfapyridine is thought by some to be superior to sulfanilamide. Specific urethritis in the male responded favorably and completely to a dosage schedule of 3 gm. of sulfapyridine a day for four days, followed by 2 gm. daily for the next six to ten days, as reported by Johnson, Leberman and Pepper (7). In gonococcic vaginitis in twenty-seven children, the lesions were healed in four days with sulfapyridine alone according to Brown (8). However, in the chemotherapy of infections caused by streptococcus and the meningococcus, sulfanilamide still remains the drug of choice.

Telling and Oliver (9) in June, 1938 first reported on the successful use of sulfapyridine in a patient severely ill with type III pneumococcus lobar pneumonia. Evans and Gaisford (10) described a mortality rate of 8 per cent in 100 cases of pneumococcic lobar pneumonia as compared with 27 per cent mortality in a control series which did not receive sulfapyridine. In February of 1939, other observers, notably Barnett et al. (11) and Flippin et al. (12), reported on the use of sulfapyridine in treating pneumonia in children and in adults. Their clinical experience was most encouraging. Numerous reports (13, 14, 15, 16) of a similar nature began to flood the literature and established the chemotherapeutic valency of sulfapyridine in pneumonia. But it is still debatable whether sulfapyridine alone will completely replace the use of antipneumococcus horse or rabbit serum.

Insofar as is known at the present time, the value of sulfapyridine lies in its bacteriostatic action only, that is, its ability to inhibit the growth of the pneumococcus—irrespective of the type of this organism. It does not neutralize the toxin of the specific polysaccharide inherent in the capsule of the pneumococcus. Ultimate recovery of the patient depends on his or her ability to develop specific antibodies in the blood plasma which will dissolve the capsule and thus produce dissolution of the infecting organism. Both of these mechanisms, bacteriostasis and bacteriolysis, are essential before phagocytosis can take place and recovery and repair ensue. Sulfapyridine alone will not hasten the development of antibodies in the blood plasma. This function is inherent in the defense mechanisms of the patient. An infection is overwhelming when the production of antibodies is inadequate. Long and Wood (17) report that sulfapyridine therapy does not alter the capsule of the organism. Successful attack on the capsule of the pneumococcus appears to be a function of the antibody only.

For these reasons if a pneumonia patient fails to respond to the administration of sulfapyridine within twenty-four to thirty-six hours of intensive chemotherapy, his defense mechanism is inadequate, i.e., it is unable to produce specific antibodies in sufficient concentration to dissolve the capsule of the organism and pave the way for phagocytosis. If infected with a typable pneumococcus for which there is available a specific serum composed of concentrated antibodies, this patient should then receive type-specific antipneumococcus serum intravenously in addition to and in conjunction with sulfapyridine. Further clinical experience indicates that it may be good judgment to administer both sulfapyridine and serum to all patients having a positive blood culture who are critically ill, and in every case where two or more lobes of the lungs are involved. If the patient is pregnant or in the first week of the puerperium, both serum and drug should be given simultaneously. In patients over forty years of age who are extremely ill, and in cases where treatment has been delayed until the third day of the disease or later, the prognosis can be definitely improved by the dual administration of the drug and the serum. In the event the pneumococcus is untypable or in cases where no type-specific antiserum is available, sulfapyridine in conjunction with routine supportive measures remains the only weapon of attack.

On admission to the hospital the patient's sputum should be typed, a blood culture taken, the urine examined, a complete blood count made, and a roentgenogram of the patient's chest taken before the drug is administered. In all cases of pneumococcal infections such as otitis media, meningitis or peritonitis, material for culture and typing should be obtained before the initiation of chemotherapy.

The administration of sulfapyridine is preferable early in the disease; dosage does not lend itself to any hard and fast set of rules. The drug is given in relatively large amounts within the shortest possible period of time to produce an adequate concentration in the blood and tissue fluids of the body. A satisfactory maintenance dose must be continued until the temperature and pulse have returned to normal and remained normal for at least forty-eight hours. If the drug is withdrawn too rapidly or discontinued too early in the course of the infection, an exacerbation of the disease may occur and the patient fail to respond to renewed administration of sulfapyridine. In such cases the patient is said to have become "sulfapyridine-fast". Moreover, a definite lag of three or even four days may occur between the initial favorable action of sulfapyridine and the development of antibody titre to the therapeutic level of efficient bacteriolysis. During this interval the physical signs of consolidation may show little, if any, change. The drug must therefore be administered continuously for several days after the temperature and pulse rate have returned to normal and the patient appears to be clinically well. This will afford his defense mechanism time to produce a sufficient number of antibodies to ensure complete bacteriolysis of the pneumococci.

The dosage requirements of an individual patient may be controlled effectively by daily estimations of the blood sulfapyridine in both the free and conjugated (acetylated) forms of the drug. As stated before, the conjugated form is inactive but toxic owing to the formation of acetylsulfapyridine crystals in the urinary tract. The free form of sulfapyridine is therapeutically active in concentrations ranging from 4 to 8 mg. per cent in the circulating blood. Abernethy, Dowling and Hartman (18) demonstrated a significant difference between the clinical response of patients having high and those with low blood levels of sulfapyridine. Their results were more satisfactory if the mean blood concentration was 6 mg. per cent or higher during the first three or four days of treatment. In thirteen children, MacColl (13) found a blood concentration of 2 mg. per cent sufficient for favorable clinical response and recommends the following dosage:

Age	*Dosage*
1 to 3 months	0.8 gm. daily
6 to 24 months	1.5 gm. daily
3 years	2.0 gm. daily
5 years	3.0 gm. daily

A somewhat similar scheme of dosage was employed by Wells and Bradley (19) in the treatment of primary pneumococcic pneumonia in fifty-nine infants under three years of age with only one fatality. A simple rule for the general practitioner to employ in infants and children is 1 grain (not gram) of sulfapyridine in twenty-four hours per pound of body weight with bicarbonate of soda, grain for grain. In pneumococcic meningitis, Hodes, Gimbel and Burnett (20) advise the use of 1 to 3 gm. daily in very young infants, increasing the dose proportionately from 6 to 12 gm. daily in older children and adults.

The following schedules of oral administration of sulfapyridine are now in general use in the treatment of adults:

In pneumococcal pneumonia, the dosage is 4.0 gm. stat. with 4.0 gm. (60 grains) of bicarbonate of soda as soon as the clinical diagnosis is established; then, 1.0 gm. every four hours (day and night) until the temperature has been normal for forty-eight hours. This is followed with 1.0 gm. and an equivalent amount of "soda" every six hours until resolution is well under way. Finally, 0.5 gm. is given four times a day until the patient is ready to leave his bed. The very first dose of sulfapyridine may be divided and given as 2 gm. for two doses four hours apart.

The intravenous administration of the soluble salt (sodium sulfapyridine monohydrate) is frequently lifesaving in patients who are critically ill with pneumococcic pneumonia, or pneumococcic meningitis or peritonitis. The soluble sodium salt may also be given by vein to patients who fail to show a satisfactory blood level of free sulfapyridine because of intractable nausea and vomiting. Parenteral injection (of the drug) is often efficacious in those patients who conjugate the drug to a high degree following oral administration of sulfapyridine. If recent surgical procedures on the stomach or intestinal tract prohibit administration of the drug perorally, sulfapyridine may be given intravenously in such cases as in postoperative pneumonia. Indeed, it is becoming almost a routine practice to administer the drug both intravenously and by mouth to pneumonia patients who are critically ill. This insures a prompt rise of the blood sulfapyridine to the level of therapeutic efficiency. A dose of 0.06 gm. per kilogram of body weight of the monohydrate sodium salt of sulfapyridine may be given by vein and, if necessary, repeated in four hours. The peroral administration of the drug in the tablet or capsule form is given in doses of 1.0 gm. simultaneously and in conjunction with the soluble salt by vein, and continued every four hours as before. This will serve both to establish and maintain an immediate effective blood level of from 5 to 10 mg. per cent. The drug in the free form is completely distributed by the blood to the body tissues within five to ten minutes after injection. By the fourth hour conjugation has begun and twelve hours after the initial injection approximately 50 per cent of the drug has been conjugated to inactive acetylsulfapyridine. Maintenance doses are therefore indicated at six to eight hour intervals, depending on the level of the blood sulfapyridine. Before repeating an intravenous dose the percentage of free and total sulfapyridine in the blood should be determined. This is a relatively simple laboratory procedure according to the method of Marshall, Emerson and Cutting (21).

Sodium sulfapyridine is freshly prepared by weighing out the required amount of the powder and dissolving this in a sufficient quantity of sterile distilled water to make a 5 per cent solution. This solution cannot be sterilized as it is thermolabile, but since it has a pH of 10.7 to 10.8 it is of itself somewhat bactericidal. It should, of course, be prepared in sterile containers as it is to be given by the intravenous route only. It should never be administered subcutaneously, intramuscularly, or intraspinally. Great care must be used to inject the solution directly into the vein; extravasation into the surrounding tissues will produce a very painful necrosis. The intravenous injection of sodium sulfapyridine should proceed slowly at the rate of 5 cc. per minute and should not be combined with transfusions or parenteral administration of glucose.

The proper intravenous use of sodium sulfapyridine produces a blood level of from 5 to 8 mg. of free sulfapyridine with great speed and certainty. This procedure, however, entails all the potential dangers associated with intravenous medication in general and those particular hazards associated with the injection of strongly alkaline salt solutions of weak acids. Marshall and Long (22) recommend that the intravenous use of sodium sulfapyridine be limited to those conditions in which oral administration of the drug is impossible or does not suffice for successful therapy.

Other methods of administration have been reported, such as the rectal route or the intramuscular injection of an oily suspension of sulfapyridine. The former does not yield satisfactory blood levels of the drug owing to slow and inconstant absorption, while the latter method is mentioned only to be condemned because of the dangers of local irritation and of oil embolism.

Blake (23) dissolved 2 gm. of sulfapyridine in 1000 cc. of 5 per cent glucose and physiological saline which had been brought to a boil. This mixture contained 0.2 per cent sulfapyridine and was given intravenously, subcutaneously and intrathecally without untoward effect. High concentrations of sulfapyridine could be obtained only by administering large volumes of this fluid (2000 cc. would be required for an initial dose equivalent to 4 gm. of sulfapyridine). Further investigation demonstrated that upwards of 25 per cent sulfapyridine could be dissolved in 50 per cent dextrose. A number of commercial drug companies are now beginning to market a glucose-sulfapyridine solution in varying concentrations for intravenous administration. It is too early to judge the value of such preparations but the clinical and biological aspects of this phase of the problem have been investigated by Finland et al. (24), who preferred to dilute the original concentrated solution tenfold in physiological saline, so that the final concentration was 2 per cent sulfapyridine and 5 per cent glucose. Their findings were not very striking and certainly the therapeutic effect of the glucose-sulfapyridine was not equivalent to the effect of corresponding amounts of sulfapyridine by mouth or of its sodium salt by vein. When given parenterally, this solution was found to be nontoxic but practically inert. When given by mouth, the effect of this glucose-sulfapyridine solution was similar to sulfapyridine, except that its absorption was delayed. At the present writing the volume of therapeutic evidence would indicate that sulfapyridine as such is best administered by mouth and, in selected cases, may be supplemented by intravenous injection of the soluble salt (sodium sulfapyridine monohydrate).

CONCLUSIONS

1. Sulfapyridine appears to be a specific chemotherapeutic agent against the pneumococcus, regardless of the type of this organism or the distribution of the infection, either lobar or bronchial. It is also a near-specific in infections caused by the staphylococcus, the gonococcus, and the bacillus of Friedlander.
2. Sulfapyridine is a more toxic and dangerous drug than sulfanilamide.
3. Other drugs may be given in conjunction with sulfapyridine as indicated by the patient's condition.
4. The only contraindication against the use of sulfapyridine is the previous history of idiosyncrasy to this drug or to sulfanilamide.
5. Sulfapyridine is slowly and irregularly absorbed.
6. Dosage is variable and can best be discussed in terms of the therapeutic blood level of the drug (4 to 8 mg. per cent).
7. Sulfapyridine is usually given by mouth in the form of tablets or capsules with an equivalent amount of bicarbonate of soda. In selected cases the intravenous administration of the soluble sodium salt of sulfapyridine, supplementing oral administration, may be lifesaving.
8. The chemotherapeutic action of sulfapyridine lies in its bacterio-

static effect only. Bacteriolysis is accomplished by the specific antibodies in the blood plasma which must be produced by the patient or introduced into his blood stream by injection of type-specific antipneumococcus serum. Both mechanisms, bacteriostasis and bacteriolysis, are essential to recovery. It is doubtful, therefore, if sulfapyridine alone or any other chemotherapeutic agent will completely replace the use of horse serum or rabbit serum in the treatment of pneumonia.

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CONGENITAL ANOMALIES*†

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The study of human fetal malformations includes not only the gross anomalies which are called monsters, but also every disturbance of structure and functional development possible. *Teratology* is the name given this subject and it is derived from the Greek *teras* meaning a monster. This paper will be confined to brief discussions concerning the history, etiology, classification, and incidence of congenital anomalies.

In using the word *congenital* only the anomalies that were present at birth are indicated. The term anomaly means any departure from the normal structure and is used interchangeably with abnormality, deformity, defect, or malformation. Heredity means the inheritance of defects from ancestry. According to Schwalbe (29), a monster is the result of a congenital alteration of one or more organs or systems of organs or the whole body, which may not be considered within the range of variation of the species.

HISTORY

Teratologic phenomena have been recorded for many centuries. Empedocles, Hippocrates, Aristotle, Pliny, and Galen used extravagant and imaginative terms in describing human malformations. According to Garrison (6), abnormalities of the fetus were recorded on clay tablets in Assyria as early as 668 to 626 B.C. The prolific Ambroise Paré wrote on monsters but many he depicted were highly fanciful. In modern times, Ballantyne, Mall, and Murphy have contributed fundamental and important investigations in this interesting field. Mythology, legend, superstition and mystery have enshrouded teratology and have indubitably impeded its study. It is no small wonder, therefore, that today there is still ignorance of the fundamental cause of human anomalies.

ETIOLOGY

While many will agree that severe malformations follow disturbances in the germ cells before fertilization, the exact cause of the disturbance remains a moot point. Petersen (27, 28) describes a seasonal trend in the conception of anomalous individuals, and reports that Hippocrates ascribed injury to the embryo to climatic conditions. Fitchet (5) suggests a damaged or translocated gene of a complex chromosome as a possible cause. Malpas (13) leans to the theory of primogeniture (the theory which claims that the first-born of a family is more apt to be defective than are the subsequent children), especially in regard to hypospadias and hydrocephalus. Macklin (10, 11) and Murphy (26) deny that in their series of cases barometric disturbances and primogeniture were possible causes of fetal abnormalities. Keller (9) believes that congenital or intra-uterine deformities very often are caused by hemorrhages into the ovum during early development. Because he was unable to prove that environment played any part in his series, and because of the frequent duplication of defects in brothers and sisters, Murphy (26) concludes that all of his data indicate disturbances in the germ cells before fertilization to be the factors primarily responsible for the production of defects. Murphy (26), Gruber (7), and many others agree that a large number of congenital anomalies are inherited. Murphy was unable to demonstrate any relationship between the frequency of malformation and such factors as contraceptive vaginal douches, pelvic disease or chronic illness before conception, wide parental age difference, month of conception, economic or social status, frequency of reproduction, illegitimacy, occupation of the father, or syphilis. He states further that the diets of the mothers of anomalous offspring were significantly deficient in calcium, iron, and vitamins B, C, and D.

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While it is admitted that the development of the ovum can be modified under experimental conditions, Murphy (26) is not convinced that spontaneously occurring abnormalities can be caused by environmental factors. He does believe his studies indicate that heredity is the fundamental cause of human fetal anomalies.

Directly opposed to this view is that of Mall and Hertwig (8), who concluded that monsters are produced by external influences upon normal ova. According to Cohn (1) and Petersen (28), skeletal defects are the result of retarded development at a certain stage in the embryologic process. From a genetic standpoint many anomalies appear to be recessive rather than dominant. Murphy's (26) investigations lead to the conclusion that gross human anomalies are the result of influences which affect the germ cells prior to fertilization.

CLASSIFICATION

Since congenital anomalies are legion, Cohn (1) and others feel that there is no reason to attempt to classify them. A great number of these are of more teratologic interest than clinical importance. However, a working flexible classification is essential for clarity, and accordingly the method given by Davis (4) is used. There are three large groups, namely, I. Anomalies of the fetus; II. Single essential monsters; III. Double essential monsters (Table 1).

I. Anomalies of the fetus. This group has three subdivisions: *heterotaxia*, which includes those cases in which there is a transposition of the viscera; *hermaphrodism*; and the *hemiterata*, those anomalies which are insufficient in extent to classify as monsters. In this latter group are found many of the common anomalies, such as harelip, cleft palate, hypospadias, polydactylia, cervical ribs, polymastia, and many other external anomalies.

TABLE 1

Classification of Fetal Anomalies (Modified from Davis [4])

I. Anomalies of the Fetus
   - A. Heterotaxia—transposition of the viscera
   - B. Hermaphrodism
   - C. Hemiterata—anomalies insufficient to classify as monsters

II. Single Essential Monsters
   - A. Teratomelus—limb defect
   - B. Teratocormus—trunk defect
   - C. Teratocephalus—head defect
   - D. Teratoprosopus—face defect

III. Double Essential Monsters
   - A. Separate twin group
     - 1. Homologous normal twins
     - 2. Acardiacus group—rudimentary or no heart
   - B. United twin group
     - 1. Parasitic
     - 2. Autositic
       - *a.* Syncephalus—united by the heads with trunks separate or fused
       - *b.* Thoracopagus—united at the thorax
       - *c.* Dicephalus—united at the pelves with the heads and often necks and sometimes part of the thorax separate

II. Single essential monsters. These major anomalies are further classified according to the portion of the body in which the gross defect is apparent. Thus, the *teratomelus* group indicates limb defect. Defects of the trunk are in the *teratocormus* group. The commonest major anomalies are seen about the head and are in the *teratocephalus* group. Many of the most bizarre malformations are found in the *teratoprosopus* or face defect group.

III. Double essential monsters. This group may be divided into two fundamental groups. The first is the *separate twin* group which includes the homologous normal twins, and the *acardiacus* group (rudimentary or no heart). The second main group is that of the *united twins*, which may be autositic or parasitic.

The terminology is at first confusing but if one considers the derivation of the prefix and suffix of each word it becomes relatively simple. As an example, one may use the word *craniorachischisis*. Breaking this word into its component parts it will be noted that *cranio* refers to the cranium, *rachi* means the spine, and the suffix *schisis* indicates a cleft or a fissure. The full meaning of the word, then, is a congenital fissure of the skull and spinal column.

The classification of terata does not include such fetal morbid states as achondroplasia and the other idiopathic diseases of the various systems. Such conditions frequently present similar problems, and perhaps some of them will be classified with the anomalies in the future when etiologic factors are understood.

INCIDENCE

In various clinics the incidence of malformations varies from less than 1 per cent to more than 2 per cent. Mall (12) gives an incidence of 0.6 per cent, while Malpas (13) gives a general incidence of malformations as 2.1 per cent. It is thus apparent that congenital anomalies are not as rare as is usually thought. However, as Murphy (26) points out, the true incidence is unknown because those anomalies which do not involve the surface of the body are usually not discovered; at death only those congenital anomalies which contributed to the death are recorded; and there is no law requiring the registration of congenital anomalies.

The group of anomalies which is brought to the attention of the orthopedic surgeon is interesting and rather frequent. According to Colonna (2), about 75 per cent of all congenital foot anomalies fall into the talipes equinovarus group. He reports that the condition is more common in males than in females. Congenital dislocation of the hip, which is usually unilateral and not diagnosed until the child begins to walk, and congenital torticollis (more frequent in males) are also mentioned by Colonna as being common congenital deformities requiring orthopedic treatment. Cozen (3) reports that true congenital dislocation of the shoulder, which is usually bilateral, is rare and the diagnosis is predicated on the absence of birth trauma and muscular palsy.

Sell (30) in studying club feet concludes that 70 per cent are in males, 60 per cent are bilateral, and 87 per cent are of the equinovarus group. He further noted a positive history of other defects in the same family in 11 per cent of his cases.

The study of the family incidence of congenital anomalies is enlightening. Murphy (26) has recently published statistical analyses of 890 congenital malformations which appeared on death certificates in Philadelphia and which were adequately confirmed. Anomalies so recorded afflict one of every 213 individuals born alive. Approximately one-fourth of the congenitally malformed are stillborn, and about 90 per cent are stillborn or die within a year of birth. The incidence of malformations is twice as high in white as in black families. In Murphy's series the frequency of birth of subsequent malformed offspring was twenty-five times greater in families already possessing a malformed child than in the general population. Malformations affecting only one part of the body were found in 77 per cent, and defects involving the central nervous system were most common. Murphy further found pyloric stenosis to be the most frequent anomaly of the gastro-intestinal tract; harelip and cleft palate the most common defects involving the musculo-skeletal system; and club foot was a rather common finding. Since duplication of defects occurred on the mother's side almost three times as often as on the father's side of the family, Murphy inferred that the characteristics of the mother have a more pronounced influence upon the offspring than do those of the father. The older the mother the more likely she is to give birth to a malformed child. Congenital malformation is more likely to afflict the child if it is fifth or later in the order of birth in the family. A child is more likely to be defective if the pregnancy follows an abortion, premature birth, stillbirth, a period of relative sterility, or during a relatively long period of reproductive inefficiency. In families with two or more defective children the defect in the subsequent offspring was identical with that in the previous defective sibling in approximately 50 per cent of instances.

During a five-year period, 1935 to 1939 inclusive, in the Department of Obstetrics of the School of Medicine, University of Maryland, there were 8365 deliveries including hospital and home confinements. The total number of fetal anomalies indexed during that time, including both minor and major terata, was 147 or 1.75 per cent. There were only seventeen major anomalies (Table 2) with an incidence of 0.2 per cent. It is interesting to note that all but one of these were defects in the central nervous system. Forty-one anomalies usually seen by the orthopedic surgeon were encountered and represented 0.49 per cent of the total. There were nine cases of club feet, and the remaining thirty-two were of polydactylism (Table 3). A number of anomalies not visible externally were found at necropsy, such as congenital heart disease (three cases), diaphragmatic hernia (one case), hydronephrosis (one case), and malposition of viscera (two cases). The fact that most of these anomalies were not found until autopsy emphasizes the observation that the true incidence of defects is not known. A few rare anomalies were observed, such as congenital stricture of the rectum, bilateral absence of the auditory canal, and external ear deformity.

TABLE 2

Major Terata in a Series of 8365 Deliveries

Hydrocephalus	10
Anencephalus	5
Sympus dipus	1
Afrontoacrodolicocephalus	1
	17

TABLE 3

Common Anomalies Usually Seen by the Orthopedic Surgeon

Polydactylism			32
Unilateral		11	
Bilateral		16	
Not specified		5	
Club Feet			9
Talipes equinovarus		6	
Bilateral	2		
Unilateral	4		
Talipes equinovalgus		1	
Unilateral	1		
Talipes calcaneovalgus		1	
Bilateral	1		
Talipes calcaneovarus		1	
Bilateral	1		
Total			41

SUMMARY

1. A brief discussion of the history, etiology, classification, and incidence of congenital anomalies is given.

2. Recent investigation in biologic statistics seems to point to the conclusion that gross human anomalies are caused by factors which affect the germ cells prior to fertilization.

3. Davis' (4) classification has been modified for the purposes of this paper, but the three main groups are as follows: anomalies of the fetus; single essential monsters; and double essential monsters.

4. Murphy (26) has made important contributions to knowledge of the family incidence of congenital anomalies. While confirmation is lacking as yet, his statistical analyses point to the following general conclusions: about 90 per cent of the congenitally malformed are stillborn or die within a year of birth; the incidence of defects is about twice as great among white as among colored families; there are about an equal number of males and females affected; from the fifth child of the family onward the incidence of anomalies is likely to rise rapidly; after the mother reaches forty years of age the incidence of abnormalities will be appreciably higher; it is more likely that a malformed child will follow an abortion, a premature birth or a stillbirth; the defect seen in the first malformed child is likely to reappear in about 50 per cent of the subsequent malformed children; and in families already having one malformed child, the birth of a subsequent malformed child will probably take place with a frequency of about twenty-five times that of the general population.

5. During a five-year period (1935 to 1939) a total of 147 abnormalities were recorded among 8365 deliveries in the Department of Obstetrics of the School of Medicine, University of Maryland. Major terata occurred in only seventeen cases, an incidence of 0.2 per cent. Of the total number of anomalies forty-one or 0.49 per cent were those usually seen by the orthopedic surgeon.

6. According to Murphy it is impossible to determine the frequency of congenital malformations in the general population because those not involving the surface of the body are usually not discovered; at death only those congenital anomalies which contributed to the death are recorded; and there is no law requiring the registration of congenital anomalies.

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ECTOPIC PREGNANCY—ANALYSIS OF FORTY CASES*†

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By definition, *ectopic gestation* is the nidation and development of the fertilized ovum in any location outside of the uterine cavity.

Extra-uterine pregnancy was apparently unknown to the ancient Greeks and Romans because no allusion was made to the subject in their literature. About 1050 A.D. an Arabian, Albucasis, described a condition that was apparently an extra-uterine pregnancy, which is, as far as is known, the first case recorded. He observed fetal parts escaping through the abdominal wall of a woman, these parts coming through a suppurating sinus.

The first operation for ectopic pregnancy was done in 1500 by a Swiss swine spayer upon his own wife. She recovered and bore several more children. The child he delivered also lived, so evidently it was an abdominal pregnancy (6).

The first operation for extra-uterine pregnancy in the United States was described by Dr. John Bard of New York in December, 1759. Only fifty-seven years ago, in 1883, Dr. Lawson Tait established the operative treatment for this condition. The first patient died, but he continued to use this method of treatment and reported a series of forty cases with one death. However, most men of that era still continued to believe that extra-uterine pregnancy was a grave condition, and when it occurred they extended all relief within the narrow boundaries of their power and calmly awaited and submitted to the inevitable end. In the same period Schauter reported 121 cases treated palliatively, with a mortality of 86.6 per cent. Purry in 1876 reported 500 cases in which there were 386 deaths, or 77.2 per cent.

The clinical material upon which this study is based consists of forty cases of extra-uterine pregnancy admitted to the Baltimore City Hospitals during a five-year period between May 1, 1935 and May 1, 1940. All were tubal pregnancies and the patients presented clinical signs and symptoms which necessitated hospital admission. They were operated upon and an ectopic pregnancy was found in every case. In many the preoperative diagnosis was correct and immediate operation was considered necessary, while others were subjected to varying periods of observation before any diagnosis was made. In spite of the different periods of observation the preoperative diagnosis was often incorrect, as will be shown. In this series of forty cases there were three deaths, a mortality of 7.5 per cent. One died of generalized peritonitis and subphrenic abscess, and two from post-operative hemorrhage.

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The incidence of ectopic pregnancy is difficult to determine because it is one of the anomalies which appear to fall indiscriminately in the field of the obstetrician, the gynecologist and the general surgeon. Schumann (1), by a comparison of the total admissions to all the hospitals in Philadelphia and the gross figures for births registered in that city, computes the incidence at about 1:300. In the Baltimore City Hospitals there is one ectopic pregnancy for every 287 births.

Fertilization of the ovum occurs invariably before it enters the uterine cavity. Its nidation and development outside of that cavity are dependent on many conditions which tend to interrupt or impede the progress of the ovum toward the uterus after it is fertilized. Such impedance usually occurs in the fallopian tubes and depends upon a variety of factors as outlined by Cosgrove (2).

1. Intratubal partial obstruction: concurrent salpingitis, postinflammatory agglutination of the tubal folds, and intratubal tumors.
2. Extratubal partial obstruction: Compression, torsion or distortion of the tube by tumors, peritubal inflammation or adhesions.
3. Lenthening or kinking of the tubes.
4. External migration of the ovum.
5. Tubal anomalies—diverticula, accessory tubes, and accessory ostia.

The occurrence of endometrial transplantation in the tube or elsewhere outside of the cavity of the uterus may also be considered as a possible etiological factor. Frankel and Schenck (3) reported that they found decidual tissue at the site of pregnancy in 62 per cent of casual specimens and in 87.5 per cent of cases where they made careful search, and believed it was present in 100 per cent of the cases. They drew the following conclusions:

1. All ectopic pregnancies, tubal or otherwise, occur because of nidation of the fertilized ovum in a locus of ectopic endometrial tissue to which the ovum is chemotactically attracted.
2. The fate of the gestation depends upon the amount of endometrial tissue present to undergo the decidual reaction and upon the depth of penetration of the ovum beyond the boundaries of this decidua.
3. All ectopic pregnancies are primary.

It may be added that salpingograms as well as tubal insufflation have been reported as being causative factors. Others have reported a hormonal disturbance preventing the proper development of the ovum and its proper movement.

In this series of forty cases two patients gave a history of having had acute salpingitis; another had known postpartum endometritis from previous admission. Twelve patients had had previous abortions. Ten patients had had appendectomies for acute appendicitis and interestingly enough there were five of these patients with pregnancy in the right tube and five with pregnancy in the left. One patient had previously had a dilatation of the cervix and curettage, another a cesarean section and oophorectomy.

From a microscopic study of the tissues removed there were eight chronically infected tubes, or 20 per cent. Perhaps too much stress has been placed upon previous infection playing the major role in the causation of ectopic pregnancies. In a review of 310 cases reported by Langman and Goldblatt (4) there was an incidence of 50 per cent of pelvic infections. A more careful study of the involved tube by the pathologist in search of an etiological factor would be of utmost benefit, especially in the search for endometrial transplants at the site of implantation, as has been suggested by Frankel and Schenck (3).

The pregnancy may occur at various points in the course of the lumen of the tube. Its location within the tube is distinguished as being respectively in the ampullar, the isthmic or interstitial portions thereof. Pregnancy in the isthmal portion of the tube is uncommon, and that occurring in the interstitial portion is relatively rare. In this series of forty cases, two were in the isthmic portion, twenty-five in the ampullar, and thirteen were not recorded. There were twenty-one pregnancies on the right side and nineteen on the left.

The tubal changes are comparable with those which occur in the uterus in cases of normal intra-uterine pregnancies. Those features which characterize tubal pregnancy are modifications such as might be anticipated in the limited space available for tubal development of the fetus. The decidua which forms in the tube is patchy and abortive. In consequence, the invading trophoblasts burrow directly into the wall of the tube and greatly weaken it. The vessels become eroded; extravasation of blood occurs and extensive hemorrhage often results. Death of the embryo usually occurs in the second or third month, occasionally later. The termination of the pregnancy may be followed by absorption of the embryo, or by the formation of a tubal mole analogous to the fleshy mole observed in the uterine abortions; or very much more frequently there is a tubal abortion or rupture (5).

Tubal abortion is estimated to occur in about 70 per cent of all cases. It seldom occurs later than the third month, this being brought about by hemorrhage which loosens the ovum from its bed. Tubal rupture is less frequent. Rupture into the broad ligament is of rare occurrence and of limited clinical importance.

It may be of interest here to quote some rare and interesting tubal ruptures. "In 1870 Pick reported the spontaneous delivery of an extra-uterine fetus by the rectum with recovery of the mother. Another such case was reported in 1876. Several such cases have been reported but perhaps the most remarkable one was reported by Chase in 1920. This was a tubal pregnancy of four months which became adherent to and ruptured into the cecum without any soiling of the peritoneum. The bright red blood was passed by the rectum. This case was operated upon seven hours after admission to the hospital. The tube and mass were removed, the cecum was closed, and the patient had an uneventful recovery. Ectopic pregnancies have ruptured even into the urinary bladder. As early as 1608 two writers spoke of fetal bones being discharged from the urinary passages. In 1717 Ebusbach described a fetus found in the urinary bladder at autopsy." (6).

The hemorrhage which occurs may be confined mostly within the tube, thus forming a hematosalpinx. More frequently there is an encapsulated mass of blood outside of the tube forming a hematocele, which tends to accumulate in the cul-de-sac of Douglas. The bleeding may occur all at one time, but more often there are repeated hemorrhages. Occasionally the entire pelvis and lower abdomen are filled with extravasated blood.

At the time of abortion or rupture the embryo dies. It may be absorbed or it subsequently goes on to various stages of fatty, carious or calcified degeneration. If secondary abdominal pregnancy can occur, progress to maturity is relatively rare and gross malformation of the child is frequently present.

At the Baltimore City Hospitals there were twenty-five ruptured tubes, three tubal abortions, nine were recorded as tube unruptured, and three were not reported. It will be noted here that the frequency of rupture was approximately eight times greater than that of tubal abortion, which is quite unlike most reports. (As mentioned previously, tubal abortion usually occurs in 70 per cent of all cases.)

Six of these forty cases had never been pregnant previously, one had been married seven weeks, another one year, three had been married three years, and one seven years. All others had at least one full term pregnancy. The largest number of cases occurred among the multiparous, as is the usual finding, and as the parity increased the incidence decreased. One of the patients had previously had six full term pregnancies and five miscarriages. There were twenty-three white patients and seventeen colored, all married except two. The youngest was nineteen years old, and the oldest thirty-eight.

Of the forty cases fifteen were diagnosed correctly (37.5 per cent), nine were suspected (22.5 per cent), and sixteen were incorrectly diagnosed (40 per cent). Of the sixteen cases missed the majority were thought to have pelvic inflammatory disease, two were diagnosed as cholecystitis, and a few others were diagnosed as incomplete abortions. Unfortunately, it was impossible to determine just how many cases were diagnosed preoperatively as ectopic pregnancy, which was not substantiated at operation. Four such cases were found, however, two being pelvic abscesses, one appendicitis, and one a ruptured graafian follicle. Most writers give between 50 and 65 per cent as missed diagnoses.

TABLE 1

RACE	NUMBER OF CASES	PERCENTAGE
Colored	17	42.5
White	13	57.5

TABLE 2

AGE	NUMBER OF CASES
19	2
20–25	9
25–30	12
30–35	11
35–40	6

The first symptoms noted were invariably some combination of missed catamenia, abdominal pain, vaginal bleeding, and sudden weakness with syncope. Table 5 shows the relative frequency of their occurrence.

The initial symptoms followed the last noted menstrual period by an interval of eighteen days to twelve weeks, the average being five weeks.

Thus one sees that a variety of symptoms may appear, but the most constant, regardless of whether tubal abortion or rupture occurs, are lower abdominal pain and vaginal bleeding. Vaginal bleeding of some amount as the initial symptom cannot be too strongly emphasized. The bleeding is characterized by a scanty dark brown or chocolate-colored discharge, which is nearly always free of clots. Occasionally, the decidual cast may have been passed. Vaginal bleeding was noted in thirty-two of the forty cases and abdominal pain was present in all. Bleeding varied from spotting of only a few hours' duration to many weeks, frequently with an interval of no bleeding. The quantity was from scant to fairly brisk hemorrhage.

TABLE 3

Relative Sterility

	cases
No previous pregnancies	6
Married 7 weeks	1
Married 1 year	1
Married 3 years	3
Married 7 years	1

TABLE 4

	NUMBER OF CASES	PERCENTAGE
Diagnosed	15	37.5
Suspected	9	22.5
Missed	16	40.0

TABLE 5

INITIAL SYMPTOMS	NUMBER OF CASES	PERCENTAGE
Pain in lower abdomen with fainting	2	5.0
Lower abdominal pain followed by vaginal bleeding	16	40.0
Vaginal bleeding followed by lower abdominal pain	9	22.5
Vaginal bleeding followed by lower abdominal pain and fainting	7	17.5
Pain in lower abdomen with vomiting	2	5.0
Pain in lower abdomen alone	2	5.0
Generalized abdominal pain, nausea, vomiting, and sharp pain in the right upper quadrant	2	5.0

The severity, localization and prostrating character of the pain in tubal rupture is too familiar to require description and if associated with syncope is pathognomonic. This was noted in nine cases and all were correctly diagnosed. One-half of the cases correctly diagnosed were admitted in shock.

It is the dull, diffuse, cramplike pain which is much more frequent, but not so well appreciated, that tests the diagnostic acuity. There may be a dull, constant pain associated with the slow tearing or stretching of the tube before rupture. Again there may be a crampy, almost constant pain caused by peristalsis of the tube and dilatation of the distal end of the tubes during a tubal abortion. Shoulder pain, unilateral or bilateral, produced by blood high in the abdominal cavity irritating the phrenic nerve endings may be misleading, unless one has ectopic pregnancy in mind. The character and location of the pain will aid in arriving at a correct diagnosis.

Thirteen, or 32.5 per cent of the patients in this series gave no history of a missed period. Of these thirteen patients, two were correctly diagnosed, two were suspected, and nine were incorrectly diagnosed. Three patients gave a history of bleeding starting at the expected time of menstruation and continuing. Two stated that the onset of menstruation was fourteen days early, and one gave a history of profuse bleeding with the previous menstrual period. From this is observed the importance of always bearing in mind the possibility of ectopic pregnancy, regardless of menstrual history. Later symptoms than those designated as initial were numerous and often clouded the clinical picture.

Nausea and vomiting were noted in thirteen patients, or 32.5 per cent. Some reported pain on defecation, five gave a history of dysuria, and five a history of a burning sensation on urination. Combinations of these symptoms were not uncommon. Two reported pain in the right upper quadrant, with radiation to the right shoulder. A few others gave a history of radiation of pain to the rectum, vagina and epigastrium. None presented the morning nausea and vomiting of pregnancy.

It is interesting to note that seven patients took drugs to initiate abortion. Quinine alone or in combination with ergot was the drug taken, and the onset of symptoms ranged from twenty-four hours to five days following the taking of these drugs. Sollman (7) reports that ergot is not an abortifacient unless dangerous doses are long continued, nor does he mention that ergot has any direct action upon tubal musculature. He is of the opinion that quinine stimulates uterine contraction. Perhaps both of these drugs stimulate tubal as well as uterine contractions in the process of pregnancy. No reference to ergot or quinine initiating tubal rupture or abortion could be found in the literature.

Duration of illness varied from one day to four-and-one-half months. The greatest number of patients dated their illness over a period of fifteen days to one-and-one-half months.

Physical findings of most interest were of abdominal and pelvic origin. These, however, by their diversity challenged satisfactory discussions. For comparative purposes the physical findings are best shown in Tables 6 and 7.

In five patients an abdominal mass was palpable. One of these was correctly diagnosed, two incorrectly diagnosed. Abdominal fluid was found in eight patients upon examination and all of these were correctly diagnosed.

Extensive abdominal tenderness prevented many examiners from feeling an enlarged uterus or pelvic mass.

It must be constantly borne in mind that any but the gentlest manipulation may result in the rupture of the already tense sac and the precipitation of a most serious clinical condition dependent on internal hemorrhage. This unfortunate occurrence happened to one patient in this series of forty cases. Following one of the several pelvic examinations done, the patient began to complain of excruciating lower abdominal pain. She became quite distended and in a short while appeared gravely ill. Her hemoglobin was checked and it had dropped from 88 per cent to 60 per cent. It was decided to operate immediately. At the operation a ruptured tubal pregnancy was found on the right side with pyosalpinx of the right tube, hydrosalpinx of the left tube, localized peritonitis, and 25 cc. of foul smelling pus. A right salpingo-oophorectomy was done and transfusions were given. The postoperative course was complicated by generalized peritonitis and subdiaphragmatic abscess. The subdiaphragmatic abscess was drained, but the patient died a few days later. This was

TABLE 6

ABDOMINAL FINDINGS	NUMBER OF CASES	PERCENTAGE
Generalized abdominal tenderness more marked in lower quadrants	12	30.0
Generalized abdominal tenderness more marked in one lower quadrant	5	12.5
Bilateral lower abdominal tenderness alone but more marked in one side	11	27.5
Unilateral lower quadrant tenderness alone	10	25.0
Tenderness in right upper quadrant alone	2	5.0

TABLE 7

PELVIC FINDINGS	NUMBER OF CASES
Enlarged uterus	6
Enlarged soft cervix	20
Pain on manipulation of cervix	14
Bulging of cul-de-sac	8
Pelvic mass	21

the only case of an infected ectopic pregnancy in the series and there are only a few case reports of this condition in the literature.

An ectopic mass may be made out by gentle palpation before actual rupture, but not before hemorrhage about the sac has altered the consistency of the tube. When demonstrated there will be marked tenderness over the mass. The ordinary signs of early pregnancy referable to the external genitalia, cervix and corpus uteri will more or less conform to those of intra-uterine pregnancy and the history of the duration of pregnancy.

After rupture, in addition to the mass lateral to the uterus there can be palpated by vagina a doughy or crepitant mass in the cul-de-sac. This is accompanied by exquisite tenderness. The uterus is commonly pushed forward by this cul-de-sac mass. Tenderness is much less striking in a hematocele than in a pelvic abscess of the same size.

Glandular changes in the breasts, with the presence of secretion, were noted in a few cases. This finding assumes considerable importance in women who have not had a previous gestation but is less reliable in parous women.

The pulse rate and temperature are not of great differential value. The former will vary with the degree of shock present; the temperature fluctuates within a range common to other conditions. In the series reported sixteen patients had a normal temperature on admission and rarely was it as high as 102°F by rectum.

The erythrocyte count is at times beneficial. In a series of cases reported by Miller (8), of all patients who received an erythrocyte count each had a definite anemia of less than 3,500,000 red blood cells. This, he reports, is of definite diagnostic value where no great amount of external hemorrhage has occurred and no prolonged suppurative process has been present. The hemoglobin varied from 30 to 90 per cent. In one-half the cases the hemoglobin was less than 75 per cent. Frequent hemoglobin determinations were often helpful in ascertaining the presence of active internal bleeding. The leukocyte count varied from normal to 26,000, with an average of 13,000. Twelve patients had a normal white cell count. The number of leukocytes depends largely on the amount of intraperitoneal blood present. A leukocytosis in the presence of a normal or slightly increased temperature points toward profuse intraperitoneal hemorrhage, being in sharp contrast to the higher temperature and lower leukocyte count of pelvic infection. Blood pressure readings are an index of the degree of shock present.

The biologic pregnancy tests may be of great value in arriving at a correct diagnosis, especially if uterine pregnancy has been reasonably eliminated. The Aschheim-Zondek test or the Friedman test gives a positive result when there is living chorionic tissue present. Therefore, the test can be positive even after the death of the fetus. A negative test merely means that no living chorionic tissue is present and does not rule out a diagnosis of ectopic pregnancy. Goldberger, Sollmon and Frank (9) reported that 32 per cent of all cases having a Friedman test gave an incorrectly negative test. Three of the patients in this series had a Friedman test, and only one was reported as being positive. The tests, therefore, are only of value when positive.

Much has been written about the sedimentation rate as a diagnostic aid. Unfortunately, the sedimentation was not done in any of the author's cases. Schiffey, Morgan and Stimson (10) conclude that "the chief value of a sedimentation rate is to differentiate an unruptured ectopic pregnancy from a pelvic inflammatory disease. In a ruptured ectopic pregnancy the sedimentation rate is as rapid as in pelvic inflammatory disease. It must be remembered that the sedimentation rate may become rapid in cases of marked anemia, or after the third month of pregnancy."

TABLE 8

TIME OF OPERATION	NUMBER OF CASES	PERCENTAGE
Immediate	15	37.5
Less than 48 hours	3	7.5
More than 48 hours	22	55.0

A colpotomy was done in only one case in which a preoperative diagnosis of pelvic abscess was made and old blood was found at operation. Following the colpotomy a laparotomy was done. No diagnostic colpotomy or needling of the cul-de-sac was done. Many writers report good results following needling of the cul-de-sac, but they all agree that it should be done carefully.

A diagnostic dilatation of the cervix and curettage was done in one case. In another case misdiagnosed as an incomplete abortion, curettement revealed decidua only and subsequently an ectopic pregnancy was found at operation. The absence of decidua does not necessarily rule out an ectopic pregnancy, since the decidua may separate and be cast off before the curettage is done. Hysterosalpingography as an aid in diagnosis has been used successfully by some gynecologists.

All of the patients in this group of cases were subjected to laparotomy as soon as the diagnosis of ectopic pregnancy was made. Table 8 gives the time of operation following admission.

Some men still disagree regarding treatment after tubal rupture. The majority, however, believe that immediate operation is better than conservative treatment. The observation of Hunter Robb that severing the ovarian arteries of pregnant bitches did not kill the animals gave rise to the conservative treatment of ectopic pregnancy. Some contend that primary rupture, while possibly serious, is usually not fatal, since an arterial twig and not a large vessel is involved. The bleeding continues until the blood pressure falls sufficiently for the formation of a clot and then the patient reacts, feeling well in a few days. During the reactive stage operation can be done more safely. However, one cannot foretell whether the reaction will take place or whether the patient will slip further and further beyond surgical aid.

The greatest menace to the patient's life is the hemorrhagic shock itself. Therefore, treatment of shock by intravenous infusion of saline, glucose and whole blood must precede the institution of other operative procedures and must be continued after the source of bleeding is controlled until the patient's condition is satisfactory enough to need them no longer. While preparation for operation is going on, the patient should be placed in the Trendelenburg position, external heat applied, morphine given, and intravenous infusion started without regard to the fear of increasing bleeding before its origin can be reached and controlled. This is not a plan of management of waiting for the patient to react before operating, but of operating in the best way as soon as one can and doing everything possible for the patient while preparing for the operation.

With regard to the operation, only enough blood should be removed from the abdominal cavity to allow good visualization of the tubes. Both tubes and ovaries should be examined carefully as there may be a pregnancy in each tube. The bleeding should be clamped as soon as it is located. The uninvolved tube should not be removed unless there is a definite pathologic lesion present. A simple salpingectomy with the removal of the ectopic mass is the operation of choice. However, at times the uterus is involved in such a way that hysterectomy is necessary. All authors agree that the appendix should not be removed as the procedure increases the mortality rate, especially if blood be present in the abdomen.

Blood transfusions, saline and glucose were given when necessary. In all there were nine autotransfusions. One patient received as much as 1200 cc. of blood recovered from her abdomen, without untoward reaction.

Table 9 gives the operations performed.

It will be noted that twenty-two of the cases had either a simple salpingectomy or a salpingectomy and oophorectomy. The second and fifth operations listed were isthmal pregnancies requiring fundusectomy. Also, eleven appendices were removed. However, none of these was responsible for the three fatal cases.

Table 10 gives the anesthetic used in this series.

TABLE 9

OPERATIONS PERFORMED	NUMBER OF CASES
Simple salpingectomy	12
Salpingo-oophorectomy with fundusectomy	1
Salpingo-oophorectomy with appendectomy	4
Salpingo-oophorectomy	10
Salpingectomy with fundusectomy	1
Bilateral salpingectomy	2
Left salpingectomy with ligature of other tube	1
Left salpingectomy, appendectomy, perineorrhaphy	1
Colpotomy and salpingectomy	1
Salpingectomy with closure of intestinal perforation	1
Salpingectomy with appendectomy	3
Bilateral salpingectomy and oophorectomy, supravaginal hysterectomy, appendectomy	2
Left salpingectomy and oophorectomy, right salpingectomy, suspension, appendectomy	1

TABLE 10

ANESTHETIC USED	NUMBER OF CASES
Nitrous oxide, ether	11
Spinal novocain	10
Spinal novocain supplemented with nitrous oxide, ether	4
Ether alone	5
Spinal pontocaine	10

Patients in extreme shock were usually given nitrous oxide and ether or ether alone, rather than a spinal anesthetic.

There were five patients with postoperative complications:

Postoperative hemorrhage which was fatal	2
Generalized peritonitis with subdiaphragmatic abscess which terminated fatally	1
Postoperative wound infections	2

CONCLUSIONS

1. The incidence of ectopic pregnancy is high and the realization of this fact is one of the greatest aids in making a correct diagnosis.

2. The importance of previous pelvic inflammatory disease as an etiological factor of ectopic pregnancy long has been overemphasized.
3. The sterility period prior to ectopic pregnancy appears to have been unjustifiably overemphasized.
4. There is no unfailing history, symptom or sign in ectopic gestation. The incidence of missed diagnosis can be materially lowered by an evaluation of all clinical and laboratory findings in each case.
5. Frequent erythrocyte counts and hemoglobin determinations as well as leukocyte counts will often aid in diagnosis.
6. The sedimentation rate and Friedman test may be of value.
7. Surgery is the best method of treatment.
8. Unless further pelvic pathology is present, only the diseased tube should be removed.
9. Colpotomy or needling of the cul-de-sac should be resorted to only as a last diagnostic procedure.
10. All patients should be watched very carefully following operation for secondary hemorrhage.

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RETICULUM CELL SARCOMA INVOLVING THE HEART AND PERICARDIUM*†

A Case Report with Autopsy

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Tumor metastasis to the heart is uncommon. When this does occur the malignancy is usually carcinoma rather than sarcoma. An involvement of the heart as the result of direct extension from some neighboring structure is even less common than true metastases.

The literature contains reports of cardiac involvement by lymphosarcoma but in the matter of reticulum cell sarcoma there is only passing mention of small areas of infiltration, particularly in the pericardium. Bengston (10) has reported a case of reticulum cell sarcoma with considerable cardiac involvement in a cow.

Kundrat in 1893 first recognized the malignant tumor of lymphatic origin classed as lymphosarcoma. It was Ewing (1), however, who in 1913 first mentioned the possibility of dividing this particular group of tumors into two distinct varieties based upon the type cell from which the malignant cells arise. He described several cases from his own material which differed from ordinary lymphosarcoma in that the cells were larger, not always round but more pleomorphic, and resembled the reticular rather than the lymphoid elements of the tissue.

Following his observation there was little interest shown in this possible separation until in the late twenties, when isolated reports on reticulum cell sarcoma began to appear. Since that time more work has been done in an attempt to classify these tumors. In the latest classifications they are considered as separate entities from lymphosarcoma (lymphoblastic).

The incidence of reticulum cell sarcoma is fairly high. Many single case reports can be found. Edling (4) reports eighteen cases and Raiford (7) reports an incidence of twenty-one cases of reticulum cell sarcoma in a series of forty-five cases of lymphoblastomatous lesions of the gastro-intestinal tract. Rosenthal et al. (9) in a consideration of 156 cases of lymphatic tumors report sixteen cases of this type. The incidence of this tumor is low in patients under twenty years, rises to a peak in the sixth decade and falls again. Eighty-four

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and five-tenths per cent of cases occur after forty years of age, while less than one per cent occur under twenty years of age [Jackson (2) and Edling (4)].

The reticulum cells of the lymph node are derivatives of the primitive mesenchymal tissue. Therefore, the cells of the reticulum cell sarcomata may show a tendency to revert to the more primordial type of tissue and varying grades of maturity or differentiation of the cells composing the tumor may be seen. This had led to much of the apparent confusion and to the many contradictory statements which today appear in the literature. It is almost impossible from reading the English and American literature to get a clear conception of the histopathology of these tumors.

Much has been written concerning the reticulum and reticular arrangement within reticulum cell sarcomata. This is primarily dependent upon the above-mentioned maturity of the component cells. The more mature and differentiated cell types will have the more characteristic reticulum which can be demonstrated by the various silver staining techniques. However, it must be kept in mind that the more primitive or undifferentiated types may show little or no characteristic reticulum. Therefore, as mentioned particularly by Gerundo and Miller (3), to depend upon the demonstration of a complete argyrophil network for the diagnosis of these neoplasms may result in overlooking the more malignant forms. These authors emphasize the fact that the formation of fibers is not a specific feature of reticulum cells but is a property of tissues derived from mesenchymal cells. It may occur almost constantly in any connective tissue tumor.

This possible variation of cytologic pattern has resulted in some attempt to subdivide the reticulum cell sarcomata into several types based upon the maturity or differentiation of the component cells. Edling (4) in a review of the problem mentions the fact that Roulet recognized three groups which he designated as immature or undifferentiated, mature, and associated or combined. He states that Ahlström adds another which he calls the polymorphocellular type.

Other reports make no effort to subdivide the reticulum cell sarcomata on the above basis. Practically all admit and even emphasize the pleomorphism of the component cells of the tumor. A rigid histopathologic division is very difficult because various portions of the same tumor may show considerable variation in the maturity of the component cells.

The histopathology as based upon a number of reported descriptions shows a tumor mass which is composed of fairly large pale cells with pale vesicular nuclei which may be crescentic, round or oval in shape. These nuclei contain finely divided chromatin, either scattered or arranged peripherally. Therefore the nuclei are light staining. Nucleoli may or may not be prominent. The cells are not tightly packed and even the more dense areas of the tumor present a fairly loose arrangement. The cells show a varying amount of cytoplasm which is slightly acidophilic and when properly stained fat droplets may be demonstrated in many of them. These cells may be phagocytic. The amount of reticulum is not constant but varies in amount even in the same tumor.

Giant cells may be few or numerous. It may be that two or more cells in a syncytial arrangement appear as giant cells. Jackson (2) says that multinucleated cells rarely may be seen. Yuile (6) mentions giant cells in varying numbers, and Raiford (7) describes considerable numbers of these cells in some of his cases. The cytoplasm stains more darkly than the cell nucleus in many of these giant forms.

The tumor tissue is fairly vascular and owing to the invasive character of the tumor, the smaller vessel walls are often seen invaded by the growth. Necrosis when present is usually of the infarct type and probably rests upon the basis of vessel invasion. Eosinophils are not present or if present are few in number. There is little tendency to fibrosis in the tumor tissue. These latter two characteristics of the growth, together with the fact that the giant cells present are definitely not of the Sternberg-Reed type (5), differentiate this tumor from the so-called Hodgkin's sarcoma.

The reticulum cell tumor is highly invasive and may involve by direct extension or metastasis any organ or system of the body. Jackson (5) stresses the fact that in some cases reticulum cell sarcoma may be an isolated lesion. He also, with Parker (8), reported primary involvement of the bone. They find that in metastatic bone involvement the lesions occur most commonly in the vertebrae and skull, while the primary bone lesions are more often seen in the long bones.

The case reported in this paper is of interest primarily because of the extensive mediastinal involvement and because of the widespread metastases.

CASE REPORT

G. F., a 40 year old white male, was admitted to the University Hospital on the service of Dr. H. M. Stein on February 11, 1939. This admission was the fourth since January 5, 1938.

Family history. The maternal grandmother and maternal great-uncle had cancers.

Past history. Childhood diseases included measles, mumps and pertussis. He suffered a head injury with concussion in 1922. There were no other illnesses, operations or injuries.

Present illness. The symptoms began in January, 1938, with substernal pain, weakness, shortness of breath and some anorexia. An outside physician diagnosed the condition as peptic ulcer and placed the patient on an appropriate dietary regime. The symptoms became progressively more severe and in May, 1938 he noticed a swelling of the neck, face and arms, and a large superficial vein on the chest. During this period he lost twenty pounds in weight. On June 5, 1938 he was admitted to University Hospital, where physical examination revealed a well-developed male whose face, neck and upper thorax were edematous. Distended veins were present over the shoulder girdles, anterior chest and abdomen, and posteriorly between the scapulae. The chest showed impaired percussion posteriorly, most marked on the left side. The breath sounds were normal. The heart was of normal size; the sounds were distant and the blood pressure at that time was 120/80, with a pulse rate of 100, and 20 respirations per minute. Mediastinal dullness was increased to the right. Each axilla contained one large and several small firm, slightly tender lymph nodes. No other nodes were palpable. Examination of the abdomen was negative. The reflexes were normal.

Laboratory data. Vital capacity 59%. Urine showed specific gravity of 1.030 and negative findings. The blood picture was as follows: hemoglobin 85% (Sahli); red blood cells 3,680,000; white blood cells 6,950, with a differential of polymorphonuclears 78%; lymphocytes 22%. A test for kidney function by the phenolsulphonphthalein method showed 80% excretion of the dye. The blood nonprotein nitrogen was 32 mg./100 cc. and the sugar 82 mg./100 cc. Electrocardiograph tracing was within normal limits.

Roentgen ray examination of the chest revealed a mass in the upper mediastinum extending to the right; both pleurae were slightly thickened. The heart was not enlarged. The esophagus was slightly displaced to the left and backward. A diagnosis of mediastinal tumor, probably Hodgkin's or sarcoma, was made. Seventeen deep radiation treatments were given over the chest. The mass diminished markedly in size and subjective symptoms disappeared. The treatments totaled 1642 R units—anterior chest 714 R units, right axilla 464 R units, and left axilla 464 R units.

During the patient's stay in the hospital his temperature ranged from 97 to 101°F. It was not of the Pel-Ebstein type and was within normal limits during the last two weeks before discharge. He was discharged on July 2, 1938 as symptomatically improved.

Following this, several readmissions to the hospital were necessary because of the return of symptoms with increased severity. He continued to lose weight and developed a persistent dry cough. In addition, fluid collected in the left pleural cavity and he later developed ascites and edema of the lower extremities. These necessitated repeated thoracenteses and paracenteses. Pathologic examination of these fluids showed no evidence of malignant cells. Additional roentgen ray therapy produced no apparent change in the size of the tumor mass.

A hypochromic anemia gradually developed. The condition of the patient persisted in following a downhill course and he died on February 20, 1939. Permission for complete autopsy was obtained.

AUTOPSY FINDINGS

Gross. The body was that of an adult white male and measured 170 cm. in length. The mouth showed some pyorrhea at the gum margins. There were no palpable nodes in the neck. The body was thin and emaciated. The abdomen was flabby and showed two midline trocar wounds. An area of sloughing 4 cm. in diameter in the antecubital fossa was present in the right upper extremity. There was pitting edema of the right lower arm and right lower leg.

On opening the thorax the mediastinum was seen to be involved by an infiltrating tumor mass which was markedly adherent to the sternum and diaphragm. The right lung hung free, except on the medial surface. The left lung was smaller than usual and adherent at the apex by fibrous adhesions and by tumor tissue to the mediastinum and diaphragm.

There was blood-tinged fluid in both pleural cavities (1250 cc. in the right and 1000 cc. in the left). The right lung was easily removed but the left lung and large mediastinal tumor mass, including the heart, aorta, esophagus and central portion of the diaphragm, had to be removed en masse.

The right lung weighed 360 gm. and showed pleural roughening over the lower lobe; on section the tissue was congested and slightly reduced in crepitancy. There were two small areas of pleural thickening showing infiltration by gray tumor tissue.

The tissue removed en masse weighed 1770 gm. There was partial collapse of the left lung. The entire organ was reduced in crepitancy and the lower lobe was non air-containing. The pleura medially, anteriorly and over the entire base was markedly thickened. On section the lower lobe was infiltrated by dense, grayish-yellow tumor tissue.

The tumor tissue in the mediastinum surrounded the great vessels and extended into the neck. It covered and obliterated the pericardial sac and appeared directly to invade the myocardium. It extended down over the medial and left portions of the diaphragm, completely involving that structure. This tumor tissue varied in thickness and measured 7 cm. at the midportion of the diaphragm. On section it presented nodules of yellowish-gray tissue, with a diffuse infiltration of all the surrounding tissue by dense gray structure. Since no normal structures could be identified, the heart was opened by following the great vessels.

The main tumor mass by direct extension invaded and replaced the pericardium, with complete obliteration of the pericardial sac and extension into the cardiac muscle. Gross section revealed the heart completely encased by dense, firm tumor tissue (Fig. 1) and no line of cleavage was present. The cardiac muscle was pale brown in color, soft and flabby. It measured 0.7 cm. in thickness in the right ventricle and 2 cm. in the left. The right auricle was somewhat dilated and the right ventricle was small. The valves appeared normal; the circumference measurements were: tricuspid 13 cm., aortic 8 cm., and mitral 10 cm. The coronary orifices were patent and the vessels showed no narrowing. Only slight superficial atheromatous deposits were found on the aorta.

The abdominal cavity contained approximately 700 cc. of watery fluid. The organs were in normal position.

The liver weighed 1230 gm. and its surface showed scattered light gray metastatic tumor nodules varying in size up to 1 cm. in diameter. The liver capsule over the dome of the left lobe was infiltrated by gray tumor tissue. The gall bladder was of normal size and partially filled with dark green bile.

The spleen weighed 100 gm. and showed nothing of note. There was an accessory spleen at the lower pole.

The adrenals together weighed 25 gm. On section, the left showed the usual brown cortex and a mass of gray tumor at one pole apparently infiltrating through the capsule. The right adrenal showed nothing of note.

Lymph nodes containing tumor tissue surrounded the pancreas but on section it showed the usual glandular structure.

The omentum was infiltrated by grayish-white tumor tissue, somewhat diffuse in its distribution. The mesenteric, coeliac and all abdominal lymph nodes were enlarged and infiltrated by dense grayish-white tumor. The wall of the intestine had lost its normal sheen throughout and appeared granular. It was darker in color than normal and on close examination small gray nodules could be seen beneath the peritoneal surface.

The peritoneum was thickened throughout the entire abdominal cavity. When opened the entire gastro-intestinal tract showed mucosal congestion and at a point near the jejunal termination there was a button-shaped ulcerated tumor mass in the bowel wall.

The left kidney weighed 470 gm. The surface was lobulated by gray masses of tumor tissue varying considerably in size. On section only very small scattered areas of recognizable kidney tissue remained. The pelvis was distorted but the mucosa was normal. The right kidney weighed 540 gm. and was similar to the left.

The urinary bladder and prostate were normal.

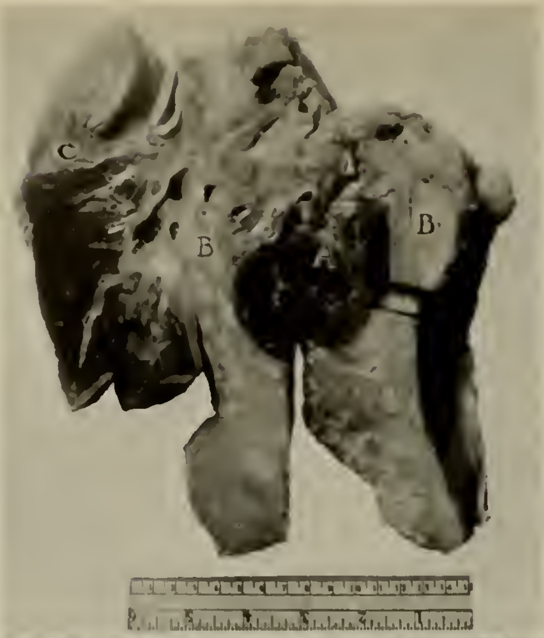
The abdominal aorta was surrounded by a mass of enlarged lymph nodes and when opened the intimal surface showed only a very slight atheromatous streaking.

Head: The brain weighed 1350 gm. and showed nothing of note in the gross. There was replacement of the bony structure of the skull above the left mastoid region involving the petrous portion of the temporal bone and the parietal bone over an area measuring 4 cm. in diameter. Here the inner table was replaced by soft yellowish tissue somewhat similar to the tumor tissue previously described.

Microscopic. Tumor: The tumor tissue was for the most part composed of a lacelike fibrous or reticulum stroma supporting pleomorphic cells. These cells were largely mononuclear but varied considerably as to size, shape and staining characteristics. There was a fair number of larger, multinucleated tumor cells in all sections. The nuclei of the tumor cells showed dark nuclear membranes. Some of them were of a paler vesicular type and others contained one or more indistinct nucleoli. The smaller cells showed comparatively little cytoplasm with the hemotoxylin-eosin stain (Fig. 2). In these the nucleus was often eccentrically placed and crescentic in shape. In the medium-sized and larger cells the cytoplasm was pale; the cell outline was very indistinct and appeared quite irregular, with suggestions of cytoplasmic projections. The giant cells of the tumor contained one to four or five nuclei, which were overlapping and often eccentrically placed. These nuclei had well defined nuclear borders. Some were dark staining, others vesicular, and nucleoli were not constant. The cytoplasm of these larger cells was darker staining and the cell outlines were not always distinct.

In fairly large areas of the growth there was little fibrous stroma, except for a fine fibrillar interlacing network which even with hemotoxylin-eosin appeared in many instances to arise from tumor cell cytoplasm (Fig. 2). With silver staining (Trelles' modification of Bielschowsky) this reticulum was seen to arise from the tumor (Fig. 3). With fat staining technique (Herxheimer) many of the tumor cells contained fat droplets. The blood vessels of the tumor were not always seen in the fibrous stroma; in many instances small, thin-walled vessels were completely surrounded by tumor cells which invaded the outer portion of the wall. Areas of the tumor showed considerable necrosis of the coagulation type seen in infarcted tissue.

Lung: These sections showed thickening of the pleura because of infiltration by tumor cells. There was considerable fibrosis. The lung tissue of the upper lobes was air containing; the capillary bed was moderately engorged, and there was some



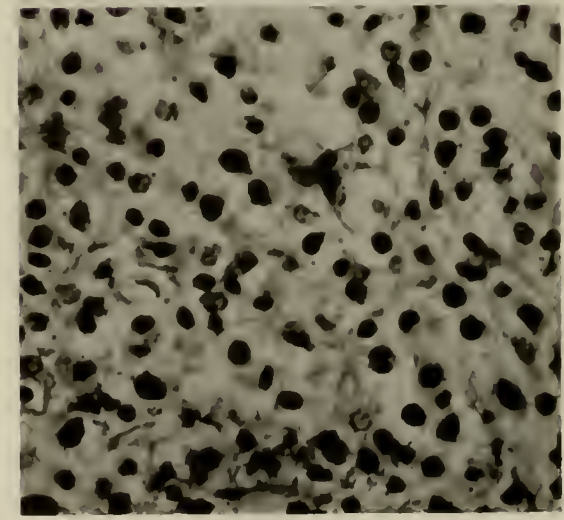
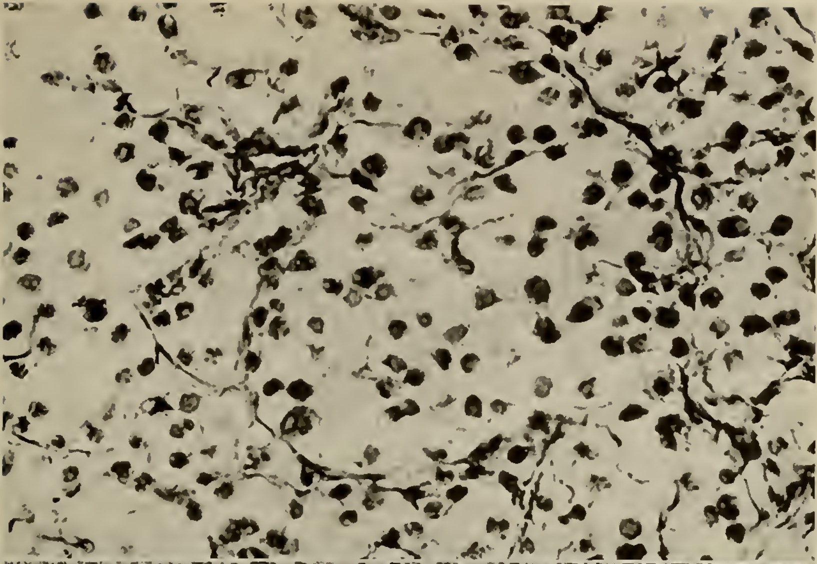


FIG. 1 (above). Primary tumor mass, posterior view, showing heart encased by tumor tissue. A. Left ventricle. B. Tumor. C. Left lung.

FIG. 2 (below). Photomicrograph of tumor tissue. Pleomorphism of tumor cells, small amount of cytoplasm in smaller cells and apparent protoplasmic cellular projections may be noted. Hematoxylin-eosin stain.



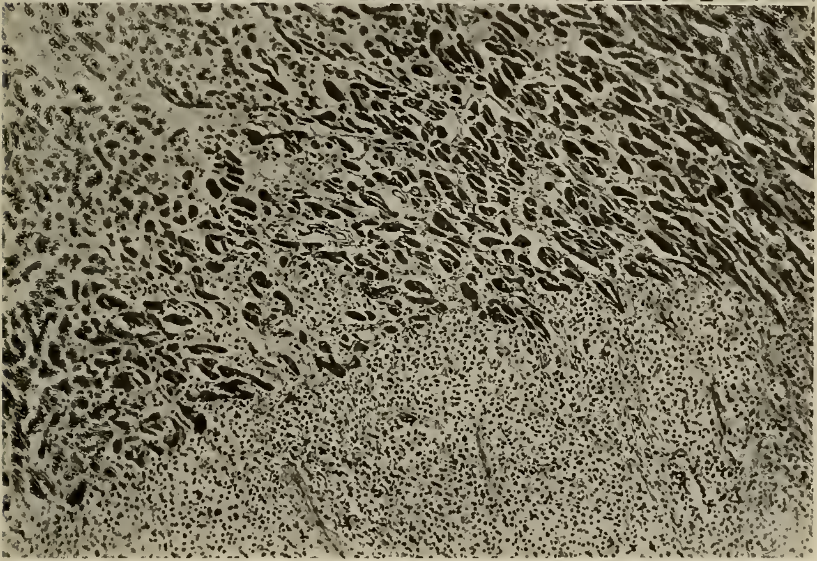


Fig. 3 (above). Photomicrograph of tumor tissue. Fine reticulum which arises from tumor cells. Trelles' stain.

Fig. 4 (below). Photomicrograph of tumor tissue replacing pericardium and invading cardiac muscle. Hematoxylin-eosin stain.

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tumor tissue present in and about the perivascular lymphatics. Sections of lung from the lower lobe near the main tumor mass were widely infiltrated with tumor tissue.

Heart: The pericardium had been replaced by tumor tissue which lay in direct approximation to the cardiac muscle. The tumor invaded the muscle both directly and by extension along the blood vessels (Fig. 4). The muscle showed considerable irregularity in staining and some loss of striation. There were areas of increased fibrosis.

Liver: There were focal areas of congestion and necrosis most marked in the central portions of the lobules. The liver tissue was destroyed and replaced by tumor tissue in certain areas.

Spleen: The spleen showed no evidence of tumor invasion.

Pancreas: The peripancreatic tissue was widely infiltrated by tumor cells and these extended by way of the interlobular septa to involve the lobules of the structure.

Left adrenal gland: This section of the adrenal gland was infiltrated with tumor tissue.

Kidney: The kidney tissue was replaced in areas by tumor tissue. Within the tumor mass occasional tubules and glomeruli could be seen. The kidney immediately surrounding the tumor was compressed and atrophic. The uninvolved kidney tissue showed cloudy swelling and degenerative changes of the tubular epithelium.

Intestine: The peritoneal surface was infiltrated with tumor tissue. The depth of infiltration varied from thickening of the peritoneum to complete replacement of the wall with ulceration of the mucosa.

Skull: Sections of tissue from the inner table at the petrous portion of the temporal bone were infiltrated with tumor tissue similar to that seen in other organs.

Brain: Sections from the first frontal convolution, left, first parietal convolution, left, basal ganglia and pons showed normal brain structure.

Anatomical diagnosis. Reticulum cell sarcoma of mediastinal lymph nodes with involvement of the pericardium and obliteration of the pericardial sac: extension to the heart, lower lobes of lungs, pleurae and diaphragm; metastases to the abdominal lymph nodes, liver, pancreas, kidneys, left adrenal gland, omentum, mesentery, small intestines and skull; bilateral hydrothorax; ascites; congestion of the lung; atelectasis, left lower lobe; cellulitis, right arm.

DISCUSSION

From the location and appearance of the tumor mass it must be differentiated from lymphosarcoma, Hodgkin's disease and thymoma. The tumor cells were large, varied much in size and shape, and showed cytoplasmic projections and reticular connections which are not the picture of lymphosarcoma. The tumor tissue showed no eosinophils, no Sternberg-Reed cells and, except in those areas receiving heavy radiation, no fibrosis. These features and the presence of a definite reticulum eliminated the diagnosis of Hodgkin's disease. All of the cells were much larger than any of the cells seen in the lymphoid thymic tissue and there was no suggestion of attempted formation of Hassall's corpuscles. Also, the wide metastatic involvement of lymph nodes tended to eliminate thymoma.

The author wishes to extend his gratitude to Dr. Harry M. Stein for permission to report this case and to Dr. Hugh R. Spencer for his assistance with the manuscript.

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MEDICAL EDUCATION*

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Mr. President, members of the Board of Instruction, candidates for graduation, relatives and friends of the graduating class: I appreciate the honor of being asked to address you this evening, and I fully realize my responsibility in the giving of this, the sixth annual pre-commencement address. I have availed myself of the opportunity of looking over the words of wisdom addressed to the graduating classes of the five previous years by Drs. Shipley, Rowland, Pincoffs, Krause, and Wise. All these addresses were good and contained much that should be told you, the graduating class of 1940. Originally I planned to quote extensively from each of the addresses but was forced to abandon this plan, with the strong recommendation that you read them carefully as published in the *Bulletin of the School of Medicine* of the University of Maryland.

My desire tonight is to bring to you some facts concerning medical education with the hope that they will help you in your postgraduate training, which you are to find as trying and as important as your years in the medical school. You have learned the importance of work, you have learned the value of honesty, and it is my purpose to point out to you through reports of the governing medical organizations of this country the way in which you can successfully carry out your further training.

The first medical school in the country, the Medical Department of the University of Pennsylvania, was established in 1765. By 1800 there were four additional colleges. The number of medical schools increased to 66 by 1860. During the Civil War twenty of these schools were discontinued, but by 1900 the number had grown to 160. The first National Medical Convention in this country was held in 1846, with the specific purpose of advancing the standards of medical education. At the second meeting in 1847 the name of American Medical Association was adopted.

In 1876 the American Medical College Association was formed, but was disbanded in 1882. The Association of American Medical Colleges was organized in 1891. It was about this time that the course in the medical schools was increased to four years. The American Medical Association collected and published statistics on the medical schools in 1900, and in 1904 it created a permanent Council on Medical Education. This Council, with the cooperation of the various medical societies, the Federation of State Medical Boards, and the Foundations, after a thorough investigation has produced tremendous improvement in the type of medical school and, more recently, in the hospitals of the country.

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This improvement has been brought about through the raising of standards of premedical work and the elimination of schools lacking sufficient facilities, so that the number of medical schools in the country has been reduced from 160 in 1900 to 67 in 1940. The importance of the hospital as a workshop for the students and recent graduates in medicine has grown steadily during the past fifty years. A recent issue of the Journal of the American Medical Association (Vol. 114, 1157–1265, March 30, 1940) contains a most instructive analysis of the hospitals in the United States. Of the 6226 hospitals now registered by the American Medical Association, 736 have assumed an educational function in accordance with the standards for hospitals approved for training interns and specialists. From recent reports it is apparent that these institutions employ annually 7654 interns, 548 general resident physicians, 230 dental interns, and 415 medical students as externs. In addition, there are many hospitals that participate in undergraduate instruction in affiliation with the medical schools. The total number of internships now available is approximately 7998, including 4956 in private hospitals and 3042 in institutions under public control.

The importance of hospital work after graduation was not fully recognized at the time I was graduated in 1904. I recall frequent discussions among the students of the fourth year class concerning the advisability of spending more time versus entering practice immediately. I later became very much interested in the discussion and in 1911 published in *The Hospital Bulletin* a short article entitled "Should All Medical Students Seek Hospital Appointments?" In this I outlined what I called an ideal course varying from a minimum of two years to a maximum of seven years, depending on the type of practice one expected to follow.

During the last twenty-five years the hospital has assumed great importance in the postgraduate training of physicians for the specialties. This method has largely replaced the former plan of attending a postgraduate school, or perhaps making a trip abroad for a few months, for which physicians received a certificate, in effect designating them as specialists. Further attempts to regulate the training of specialists were made by medical societies representing the various specialties, following a plan started by the American Ophthalmological Society, the Section on Ophthalmology of the American Medical Association, and the American Academy of Ophthalmology and Otolaryngology in 1913. In this year a committee was appointed to discuss the formation of a board, and in 1916 after much preliminary work this board was organized as the American Board for Ophthalmic Examinations, later changed to the American Board of Ophthalmology. It was incorporated on May 3, 1917.

As other specialties formed boards similar to the American Board of Ophthalmology, the need for some supervising and coordinating control led to action by the American Medical Association in 1933, authorizing the Council on Medical Education and Hospitals: (1) to formulate standards of administration, based on those of the American Board of Ophthalmology, of Otolaryngology, of Gynecology and Obstetrics, and of Dermatology and Syphilology; and (2) to recognize officially new boards meeting these standards.

The chief functions of the American Board of Ophthalmology were stated as: (1) to establish standards of fitness to practice ophthalmology, and to cooperate with hospitals and graduate schools of medicine; (2) to arrange and conduct examinations to test the qualifications of those who practice ophthalmology, and to confer certificates upon those who meet the standards as established by the Board; (3) to act as preceptors for prospective students of ophthalmology. Through their efforts the American Board of Ophthalmology has accomplished a great deal and, though they assume no powers of regulation over the ophthalmologists of the country, their certificate is recognized as indicating a satisfactory standard for ophthalmology. The American College of Surgeons, for example, recognizes the certificate of this Board as evidence of academic fitness in ophthalmology.

In the present plan for postgraduate training, the various boards are playing a most important part. The plan is a sound one because it has gradually and carefully, with the cooperation of all the important medical societies and with the thought of leaders in the various special branches, evolved its present system. In a directory compiled in 1939 by the Advisory Board for Medical Specialties, there are listed 14,000 specialists certified to date by the American boards. The directory was designed to coordinate the work of the several special boards. In it you will find much valuable and necessary information for your further training. Of chief interest to you at the present time is the section on qualification of candidates. Under the heading of general qualifications, professional standing and special training, there is outlined for you the work which you will be required to do to qualify for examination before the board. At first sight this may appear to you as dictatorial, or you may feel it places on you a heavy burden after your long years of university and medical school training. The diploma which you receive tonight still permits you, as it did in the beginning of this medical school, to practice medicine, and it can only be taken from you for very serious, perhaps even criminal, offenses. By following the recommendations of the various boards, however, you will be prevented from groping amid the difficulties, uncertainties and perplexities in the beginning of your postgraduate medical training. Many of you will comply with the minimum requirements of the Board of Surgery, for example, in spending a period of five years in your hospital work, or it is hoped you will be sufficiently impressed with the fairness of the recommendations to avoid practice in a special line if you have not met the minimum requirements of training.

Let us look for a moment to conditions in our own medical school and hospital. The fact that we are one of the oldest medical schools in the country is of but historic interest. The fact that we are improving in the present medical trend is of importance for the future. Much has been said of our glorious past, but I am reminded of the remark of an alumnus twenty-five or thirty years ago who said, "I am not interested in the type of University of Maryland Medical School attended by my father or grandfather; I am interested, however, in the type of University of Maryland Medical School which is to be attended by my sons and grandsons."

You in your medical training have profited by the efforts of those who have been working earnestly in this old institution to make it a lasting and useful one. After all, to be one of sixty-seven medical schools in the whole United States, to have survived the period of reorganization, and to be in a healthy, growing state today is reason for pride, but a more important reason for further effort of all of us. I have spoken of the importance of hospitals in medical education. The facilities of the University Hospital today more than meet the modern requirements. You of this graduating class have enjoyed these facilities and some of you are to serve upon the house staff. It is hoped you will remain there until you have fulfilled the requirements of the examining board in the field which you will select for practice.

From the beginning, the University of Maryland has prided itself on the practical training given its students. In the various reports of the School of Medicine one finds frequent mention of this fact and it is fair to say that the school in the past has been slow to change from the practical clinical course to the more modern research plan of medical education. For many years, however, the advisability and even the necessity for the change has been evident, and every effort has been made by the staff of the School of Medicine and Hospital to carry out such research as the facilities would support. We are no longer satisfied to cling to the principle expressed in the Forty-Fourth Annual Circular of the School of Medicine (1851): "The history of the monstrous tumors which develop themselves in the Chinese at Canton or Peking has but little real value for the practitioner on the banks of the Ohio. The attention of the student, therefore, is directed not to those things which are intricate, curious, and rare, but to those with which he will have to deal in daily practice."

Yesterday there was dedicated to the use of the School of Medicine of the University of Maryland a complete modern building known as the Bressler Research Laboratory. This truly marks a new era in the School of Medicine. It is particularly fitting that this building, with a substantial fund for its maintenance available within a few years, is the gift of an alumnus of the School. Dr. Frank C. Bressler, a graduate of the College of Physicians and Surgeons (Class of 1885), a part of the University of Maryland School of Medicine since 1915, has set an excellent example which it is hoped will be followed in the future by many of the graduates. An inspection of the building will convince you of the tremendous advantage which this building is to be to you, but I am sure that you will also be impressed by the tremendous task it places upon those responsible for its maintenance and proper use. There is at the present time a nucleus of research workers, but from your group, and from similar groups of the next few years, earnest, sincere research workers must be found.

For the support of this work in the immediate future funds must be provided and for some time a quiet campaign has been carried on among the alumni known as the Bressler Research Alumni Campaign. I am sure that as recent graduates you will want to do your part as a worker or with financial contributions to the research activities of the University of Maryland School of Medicine. It is very significant that there are at the present time 5114 living graduates of the University of Maryland School of Medicine. Few, if any, in this group are in a position while living or after death to do as Dr. Bressler did in the bequest of more than a million dollars for the sake of medical research in the University of Maryland. The research fund, however, offers an opportunity for every alumnus to support the work so substantially started by Dr. Bressler.

It is not sufficient for the alumni to say that it is the duty of the

State to support the institution. On the contrary, those responsible for the distribution of State funds are bound to be influenced by the effort made by the alumni group. There is no reason why a State-supported institution should not receive funds from individuals. The Bressler Building is evidence that a memorial bearing the name of the donor can be established in this State-supported institution. The Medical Alumni Association at the present time is in a very healthy state. We are all encouraged by the reports received at the Annual Meeting, and further encouraged by the report of Acting Dean Wiley which mentioned, in addition to many other facts, the donation by the Medical Alumni Association of a sum of $1200 for the support of a scholarship in the School of Medicine.

From this time on you are going to be asked to perform many services. I am merely stressing the service to your Alma Mater. The community will demand your service, individual cases will make demands far beyond your strength, but unless you can meet these demands you will not realize the full success of medicine, for in the last analysis this must be in the pleasure of service. The compensations, however, are many and it is unnecessary for me to enumerate them here, but in serving the community we are serving ourselves. I am reminded of a prominent surgeon who closed his community hospital during the last war and volunteered for service in France. When the armistice was signed he remained in France with many others, but very anxious to return to the States to reopen his hospital. He was repeatedly heard to say that he must return because his community needed him. In the large mess hall one morning a medical officer called to a friend and said, "John, I must return home." "Why," said John, "does your community need you?" "No," said the doctor, "but I need my community." Some community is waiting for you. It needs you but, my, how you will need it after five or six more years of hospital training!

PROCEEDINGS

of the

University of Maryland Biological Society

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Department of Botany
College Park, Md.

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ONE-HUNDRED-AND-FIFTH PROGRAM MEETING

The One-Hundred-and-Fifth Program Meeting was held on Tuesday, April 16, 1940 in Gordon Wilson Memorial Hall.

Dr. Melvin F. W. Dunker, William R. Warner Fellow in Pharmaceutical Chemistry, University of Maryland School of Pharmacy, read a paper entitled "On Aliphatic Amines." On the same program a paper on "The Effect of Testosterone Propionate on the Rat Testis" was read by Dr. H. S. Rubinstein of the Research Laboratory, Surgical Division of Sinai Hospital, and Mr. A. A. Kurland of the School of Medicine, University of Maryland. Abstracts of these papers follow.

ON ALIPHATIC AMINES*†

Melvin F. W. Dunker, Ph.D.

An extensive survey of the literature appearing on the simple aliphatic amines with special reference to their physiological activity has been made. Few generalizations can be presented. The bulk of the work on physiological activity has been done on the three methylamines, ethylamine, n-butylamine, and isoamylamine.

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* Read at the meeting of the University of Maryland Biological Society, April 16, 1940.

† Willam R. Warner Fellow in Pharmaceutical Chemistry, University of Maryland School of Pharmacy.

Even here it is difficult to make any definite correlation because of the lack of uniformity in experimental animals, procedures and methods of expression. In many instances also, the purity of the compounds is open to question; no statement of purity may be made or wide ranges in boiling points allowed. Pressor studies have shown activity to begin with propyl or butylamine and to increase to a maximum in hexylamine, and then to decline with further increase in chain length. The toxicity studies have not been sufficiently extended and are not uniform enough to allow any general statements. Several interesting studies, such as the effect of amines in producing gastric ulcer, the production of hemorrhages when administered orally for a period of time, the antiseptic action of the higher amines, and the antispasmodic properties of certain unsaturated 8 and 9 carbon amines, were commented upon. A few paths of study that promise interesting results were presented.

THE EFFECT OF TESTOSTERONE PROPIONATE ON THE RAT TESTIS*†

H. S. Rubinstein and A. A. Kurland
BALTIMORE, MD.

Three groups of male albino rats with appropriate litter mate controls were used for this study. Animals in Group 1 received either 20 gamma, 1 mg. or 2.5 mg. testosterone propionate (Perandren-Ciba) intraperitoneally daily for ten days beginning at twenty-two days of age; animals in Group 2 received either 5, 10, 20 or 50 gamma subcutaneously daily for ten days beginning at twenty-two days of age; and animals of Group 3 received either 50 gamma or 2.5 mg. intraperitoneally daily, except Sunday, beginning at twenty-six days of age. Animals of Groups 1 and 2 were sacrificed when they were thirty-two days old; those of Group 3 were sacrificed at eighty days of age.

It was observed that body weight remained unaffected in all animals except in those receiving extended treatment with 50 gamma daily, when it was significantly increased by 21 per cent. The penes, prostates and seminal vesicles were significantly increased with all dosages used but, unlike the prostates which maintained a progressive increase with all progressively larger doses, the penes and seminal vesicles reached their peaks at lower dosage levels.

The testes of the 5 gamma animals became significantly heavier, while those of animals receiving 10 gamma were unchanged in weight. Increased dosage caused a progressive depression which reached as low as minus 51 per cent with 50 gamma daily in the younger animals. All doses larger than 50 gamma in the younger group depressed testicular weight, but the degree of depression was inverse to the size of the dose. In the older animals, 50 gamma had no weight depressing effect on the testes although it was large enough to cause significant growth of all accessory sex organs. The larger dosage of 2.5 mg. did lower testicular weight significantly.

Microscopically it was observed that in spite of testicular weight changes only those animals receiving 2.5 mg. daily (either for ten days in younger animals or for more extended periods in the older animals) displayed degenerative changes in their testes.

The dosages used by others and the dosages in these three groups were analyzed on the basis of concentration per gram body weight and it was found that initial large doses, if continued, because of the growth of the animal finally become relatively small. The question of dosage was considered and it is felt that previously reported small doses were still quite large when compared to the small doses in this study.

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* From the Research Laboratory, Surgical Division, Sinai Hospital.

† Read at the meeting of the University of Maryland Biological Society, April 16, 1940.

The modus operandi of testosterone propionate was analyzed and it is felt that among other things four factors influence its effect, namely, the size of the dose, the duration of treatment, the age (body weight) of the animal, and the secondary sex organ response. Depending upon these and perhaps other as yet undetermined factors, the final concentration of testosterone propionate in the blood regardless of initial dosage will be either small and still physiological, or pathologically large.

The discrepancies in existing literature appear to be caused by differences resulting from these different final concentrations.

ONE-HUNDRED-AND-SIXTH PROGRAM MEETING

The One-Hundred-and-Sixth Program Meeting was held on Tuesday, May 14, 1940 in the Engineering Auditorium at College Park, Maryland. Dinner was served in the University dining hall.

Dr. Eduard Uhlenhuth, Professor of Anatomy, School of Medicine, University of Maryland, read a paper on "Peculiar Effects of Pilocarpin and Adrenalin upon the Specific Action of Thyreoactivator." Dr. Ronald Bamford, Associate Professor of Botany of the Department of Botany, College Park, also took part in the same program. His subject was "Hybridization and Chromosome Number in Gladiolus."

HYBRIDIZATION AND CHROMOSOME NUMBER IN GLADIOLUS[*][†]

RONALD BAMFORD, PH.D.

The problem of hybridization and chromosome number in *gladiolus* has been receiving attention for seven years. When previous scattered reports on hybridization were interpreted in the light of the author's studies on chromosome number it seemed that the two were correlated. In other words, the hybrid was or was not produced, depending upon the proximity of the parents to each other as measured by chromosome number. Several thousand attempts have been made at crossing all types of varieties and species, and it has been found that, while the number of progeny may be reduced in wide crosses, they most always can be made. Furthermore, in certain hybrids which should be sterile because of their parentage, secondary and tertiary hibrids have been obtained and the chromosome number of these seem to have no connection with the basic number for the genus. Present studies indicate that the author is dealing with some apomictic phenomena as well as sexual reproduction.

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[*] From the Department of Botany, College Park, Md.

[†] Read at the meeting of the University of Maryland Biological Society, May 14, 1940.

The following is an abstract of a paper presented at a previous meeting.

SOME BIOLOGICAL PROBLEMS DEPENDING ON VARIATION IN POPULATIONS*†

C. A. Morrell

OTTAWA, CANADA

From a number of examples selected from nutritional and pharmacological data, the extent and types of some variations commonly occurring in populations are demonstrated. The two main types of variation considered are aperiodic variation and individual variation. In the past, and to a large extent even today, these variations have been virtually ignored by many biological investigators, or only a pretense made in considering them. It is pointed out that the reliability of biological measurements can be assessed by the use of a few simple calculations involving the determination of the mean, the standard deviation and standard error. If these simple statistics are used with a proper degree of caution, not only may unjustified conclusions be avoided but some measurements can be transformed from a qualitative to a quantitative type.

Quite apart from their usefulness in the determination of possible errors of measurements, the methods have interesting applications in problems of biology and pharmacology. Examples show the results of inbreeding on the reaction to a drug, on the occurrence of dynamic or static variation in a population, and on the analysis of mixtures of toxic materials.

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* Senior Pharmacologist, Laboratory of Hygiene, Department of Pensions and National Health.

† Read at the meeting of the University of Maryland Biological Society, March 11, 1940.

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The names listed above are officers for the term beginning July 1, 1940 and ending June 30, 1941.

PRE-COMMENCEMENT EXERCISES

May 31, 1940

The Lyric, Baltimore

ORDER OF EXERCISES

I. The Procession: *The Coronation March*, Meyerbeer; *Pomp and Circumstance*, Elgar.

II. Invocation: Rev. Boyd R. Howarth, Rector of the Memorial Protestant Episcopal Church.

III. Greeting: H. C. Byrd, B.S., LL.D., Sc.D., *President, University of Maryland.*

IV. The Address: Charles Bagley, Jr., M.D., *Professor of Neurological Surgery, University of Maryland.*

V. Introduction of Medical Council: By H. Boyd Wylie, M.D., *Acting Dean, School of Medicine.*

Arthur M. Shipley, M.D., Sc.D., *Professor of Surgery*
Hugh R. Spencer, M.D., *Professor of Pathology*
H. Boyd Wylie, M.D., *Acting Dean of the Faculty and Professor of Biochemistry*
Carl L. Davis, M.D., *Professor of Anatomy*
Maurice C. Pincoffs, B.S., M.D., *Professor of Medicine*
Frank W. Hachtel, M.D., *Professor of Bacteriology*
Eduard Uhlenhuth, Ph.D., *Professor of Anatomy*
Clyde A. Clapp, M.D., *Professor of Ophthalmology*

JOHN C. KRANTZ, JR., PH.D., *Professor of Pharmacology*
WALTER D. WISE, M.D., *Professor of Surgery*
J. MASON HUNDLEY, JR., M.A., M.D., *Professor of Gynecology*
WILLIAM R. AMBERSON, PH.D., *Professor of Physiology*
LOUIS H. DOUGLAS, M.D., *Professor of Obstetrics*

VI. INTRODUCTION OF GRADUATES AND THE AWARD OF HONORS: DR. H. BOYD WYLIE, assisted by DR. JOHN E. SAVAGE.

CLASS ROLL

Glenn Horner Algire
S. Ralph Andrews, Jr.
William Charles Arney
John Cletus Baier
Walter Levi Bailey
Daniel Cleveland Barker
Edmund George Beacham
Harold Paul Biehl
Jesse Nachlas Borden
Irving Carlton Brinsfield
Lester Harold Caplan
Weldon Porter Chandler
Robert Henry Clifford, Jr.
John Totterdale Cole
Paul Harvey Correll
Louie Samuel Daniel
Edwin Oliver Daue, Jr.
Joseph De Luca
Charles Frederic Dent
Leonard Vincent Don Diego
William Carroll Duffy
James Richard Dwyer
James Albert Freeman, Jr.
William Hammond Fusting
William Farrow Gassaway
Robert Louis Gibbs
Irving Van der Veere Glick
Walter Raleigh Graham
Luis Roberto Guzman-Lopez
Morton Hecht, Jr.
Emil Heller Henning, Jr.
Albert Heyman
Elizabeth Louise Hooton
Daniel Hope, Jr.
Susana Igartua-Cardona
Benjamin Harrison Inloes, Jr.
William Parks Jamison
Louis Cecil Jorgensen
James Roscoe Karns
Julian Gilbert Kirchick
Schuyler George Kohn
Edward Louis Joseph Krieg
Albert Alexander Kurland
Robert Eshelman Lartz
William Soy Ming Ling
William Cook Livingood
Frank Ford Loker
Harry Pearce Maccubbin
Simeon Van Trump Markline
Clarence Wilbur Martin
Alfred Richard Maryanov
Daniel Hutchinson Mathers
Harold Francis McCann
James Edward McClung
William Dennis McClung
George Croxton McDaniel
William James McKinnon
Forest Chauncey Meade
Joseph Miceli
Edward Louis Molz
Frederick Elbert Murphy, Jr.
William Travers Muse
George Roger Myers, Jr.
James Francis O'Hara
Guillermo Pico Santiago
Ross Zimmerman Pierpont
Robert Toms Pigford
William Platt
Arthur Edgar Pollock
Leonard Posner
John Costello Pound
Charles Martin Rhode
Conrad Louis Richter
Raymond Clarence Vail Robinson
Donald James Roop
Carl Eliot Rothschild
Thomas Edgie Russell, Jr.
Philip Joseph Russillo
George Gerard Schlesinger
Joseph Wright Sloan
James Brady Smith
Ruby Arden Smith
Orlando John Squillante
Howard Nehemiah Stayton, Jr.
William Joseph Supik
Louis Haberer Tankin
Alexander Frank Thompson
Samuel Tompakov
Wilfred Henry Townshend, Jr.
William Trevor
William Carryl Triplett
Merton Theodore Waite
William Earl Weeks
Jesse Lee Wilkins
Herman Joseph Williams
Richard Talbot Williams
Harry Thomas Wilson, Jr.
William Irwin Wolff
James Rhodes Wright
Solomon Bernard Zinkin

HONORS

SCHOOL OF MEDICINE

University Prize Gold Medals

James Roscoe Karns William Irwin Wolff

CERTIFICATES OF HONOR

Joseph Wright Sloan
Lester Harold Caplan
Carl Eliot Rothschild
Samuel Tompakov
William Soy Ming Ling

The Dr. A. Bradley Gaither Memorial prize of $25.00 for the best work in genito-urinary surgery during the senior year—Charles Martin Rhode

The Samuel M. Shoemaker Memorial prize of $25.00 for the best essay on "Milk in Relation to Public Health" written by a student in the senior class—Edward Louis Molz

VII. ADMINISTERING OF HIPPOCRATIC OATH: DR. ARTHUR M. SHIPLEY, *Professor of Surgery.*

VIII. BENEDICTION: REV. BOYD R. HOWARTH, *Rector of the Memorial Protestant Episcopal Church.*

IX. THE RECESSION: *March of the Priests*, Mendelssohn.

THE MARSHALLS

Chief Marshall, HARRY C. HULL, M.D.

JOHN C. DUMLER, B.S., M.D.
FRANK K. MORRIS, A.B., M.D.
HARRY V. LANGELUTTING, A.B., M.D.
HENRY F. ULLRICH, SC.D., M.D.

COMMENCEMENT EXERCISES

JUNE 1, 1940

Ritchie Coliseum, College Park

COMMENCEMENT PROGRAM

CONCERT—MARCH—*Americans We*—Filmore.

OVERTURE—*Martha*—Flotow.

SELECTION—*Faust*—Gounod.

WALTZ—*Ciribiribin*—Pestalozza.

EXCERPTS—*Maytime*—Romberg.

INTERMEZZO—*In a Chinese Temple Garden*—Kettlebey. (The University of Maryland Band).

OTTO SIEBENEICHEN, *Director*

THE ACADEMIC PROCESSION—PROCESSIONAL MARCH—*Tannhauser*—Wagner. (The University of Maryland Band).

INVOCATION—THE RIGHT REV. WILLIAM MCCLELLAND, D.D., Bishop of Easton.

MUSIC—*My Maryland*—Audience.

ADDRESS—"Parallel Lines of Defense," DR. THOMAS PARRAN, JR., Surgeon General, United States Public Health Service.

MUSIC—*America*—Audience.

CONFERRING OF HONORARY DEGREES, HONORARY CERTIFICATES, AND DEGREES IN COURSE—PRESIDENT H. C. BYRD.

MUSIC—*The Star Spangled Banner*—Audience.

BENEDICTION—THE RIGHT REV. WILLIAM MCCLELLAND.

THE ACADEMIC RECESSION—RECESSIONAL MARCH—*The Man of the Hour*—Filmore. (The University of Maryland Band).

REUNIONS

CLASS OF 1910, COLLEGE OF PHYSICIANS AND SURGEONS

The thirtieth reunion of the Class of 1910 of the College of Physicians and Surgeons took place on May 30, 1940. A reception was held at the University Club preceding the annual banquet of the Medical Alumni Association. After the banquet the members convened at the Lord Baltimore Hotel for a final get-together. Those present were: Drs. Walter D. Blankenship, Harrison L. Brehmer, John J. Burne, Denis J. Cronin, Gaile W. Kahle, Ernest McDede, Charles W. Maxson, Alexander M. Maysels, Ellwood T. Quinn, Conrad F. Sayre, Herman Seidel, George A. Seymour, Letcher E. Trent.

Dr. Charles W. Maxson of Baltimore was in charge of arrangements for the reunion.

CLASS OF 1920 OF THE SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND

For the Class of 1920 the twentieth reunion is now history and it was a most pleasant one for all those who were present. Of the fifty-three members on the alumni list, twenty-eight returned and eight wrote letters regretting their inability to attend but extended their greetings to all.

All of the visiting members were, to say the least, greatly impressed with the new Bressler Research Laboratory and enjoyed all of the activities. The returned classmates were entertained by Dr. and Mrs. Howard M. Bubert at their home and then sojourned to the Lord Baltimore Hotel for the Annual Banquet. A reception room was set aside for the class and soon all were in earnest conversation; acquaintances were renewed and many pleasant memories recounted.

The local committee has since received many appreciative letters in which the writers told of the enjoyable time they had and expressed their pleasure in looking forward to the next reunion.

The following is a list of those who were present:

Drs. Philibert Artigiani, Lynn H. Brumback, Howard M. Bubert, Nathan J. Davidov, Louis C. Dobihal, John J. Erwin, Leon Ginsberg, Frederick A. Holden, Z. Vance Hooper, Albert H. Jackvony, Edward L. Kaufman, Earl P. Knotts, William Lueders, Jr., Waldo K. McGill, William Francis Martin, George C. Medairy, John W. Metcalf, William J. B. Orr, Clayton C. Perry, Daniel J. Pessagno, J. Morris Reese, Lawrence J. Rigney, Jr., Henry Sheppard, Jr., James W. Skaggs, Fred B. Smith, Howard Lee Tolson, Thomas F. White, Israel S. Zinberg.

CLASS OF 1930 OF THE SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND

The Class of 1930 held its tenth reunion at the Lord Baltimore Hotel on May 29, 1940 from 5:30 to 7:30 P.M. The only speech was the one made by the President, Dr. Kenneth Benfer.

The alumni of this class not only had an enjoyable time but found it quite interesting to swap experiences and renew friendships. A large number of the members of the class attended and many wrote of their disappointment in not being able to be present. Dr. Daniel E. Forrest, Jr. of Hillsboro, N. C. telephoned during the cocktail party to extend his greetings and express his regret at being unable to attend. Those who attended the reunion were:

Drs. William Belinkin, Kenneth Benfer, Joseph Blum, Irvin Cohen, Archie Cohen, Clay Durrett, Wylie Faw, Samuel Fisher, Abraham Garfinkel, Harry Gerner, Paul Gersten, Emil J. Hildenbrand, Rollin Hudson, Abraham Kleinmen, Abraham Kremen, Thomas Magovern, G. Bowers Mansdorfer, Benjamin Miller, James Miller, Isaac Miller, Egbert Mortimer, Nathan Needle, Duncan Owen, Zack Owens, George Sawyer, Carl Thompson, Aaron Werner, Ralph F. Young, Samuel Zeiger.

CLASS OF 1935 OF THE SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND

Sixty-three members of the Class of 1935 held their fifth reunion on May 29 and 30, 1940. This is the largest class reunion in the history of the School of Medicine and was attended by members from California, Utah, Michigan, North Carolina, South Carolina, Virginia, West Virginia, Delaware, Pennsylvania, New York, New Jersey, Connecticut and Maryland. Several of the senior members of the Faculty were guests of honor at a dinner held by the class on May 29. On the following day a large contingent of the class was present at the dedication of the Bressler Research Laboratory and later in the evening attended the banquet of the Medical Alumni Association.

The loyal spirit manifested by the members of the Class was most gratifying to those in charge of the arrangements and the following permanent reunion committee was elected to make plans for an even larger reunion in 1945:

Harry M. Robinson, Jr., Chairman
Ernest I. Cornbrooks
Howard Mays
Karl Mech
John W. Albrittain
F. E. Knowles

THE 133RD ANNUAL BANQUET

The 133rd Annual Banquet of the Medical Alumni Association of the University of Maryland was held on May 30, 1940 at the Lord Baltimore Hotel, Baltimore. The speakers on the program were as follows:

Dr. H. C. Byrd, President of the University of Maryland
Dr. J. Ben Robinson, Guest Speaker
Dr. John C. Krantz, Jr., Guest Speaker
Frank Ford Loker, President of the Senior Class
Dr. H. Boyd Wylie, Acting Dean of the School of Medicine
Dr. Arthur Hebb, President of the Medical Alumni Association, Toastmaster

In addition to the speakers, the following were the guests of honor: President H. C. Byrd, His Excellency Herbert R. O'Conor, Governor of Maryland, The Honorable Howard W. Jackson, Mayor of Baltimore, members of the Board of Regents, graduates of the Class of 1885, and graduates of the Class of 1940.

REGISTRANTS FOR SPRING ACTIVITIES

The following alumni registered during the Spring Activities:

Drs. Ezequiel Martinez-Rivera, San Juan, P. R.; L. L. Sawyer, Norfolk, Va.; M. W. Myers, Warren, Ohio; A. H. Riordan, Indian Orchard, Mass.; Michael J. Egan, Savannah, Ga.; B. M. Stein, Hempstead, N. Y.; C. C. Zimmerman, Cumberland, Md.; C. W. Lurting, Pittsburgh, Pa.; Albert A. Naumann, Springfield, Mass.; Albert H. Jackvony, Providence, R. I.; Fred Fernald, Nottingham, N. H.; W. W. Hala, Long Island City, N. Y.; Abraham Garfinkel, Flemington, N. J.; Joseph Nataro, Newark, N. J.; Emil Hildenbrand, Washington, D. C.; B. H. K. Miller, Philadelphia, Pa.; Frederick E. Knowles, East Orange, N. J.; T. Richard Paganelli, New York City; H. H. Simpson, Elon College, N. C.; O. W. Renz, Erie, Pa.; M. R. Bruin, Los Angeles, Calif.; C. H. Moses, Sharon, Pa.; Raymond Sekerak, Bridgeport, Conn.; Peter Pileggi, Bridgeport, Conn.; William Belinkin, New York City; A. L. Hyatt, Kinston, N. C.; J. M. Silverstein, Millburn, N. J.; B. A. Chapman, Springfield, Vt.; Harold H. Fischman, Newark, N. J.; Winfield Kohn, New York City; Paul F. Gersten, Flushing, N. Y.; Aaron S. Werner, Brooklyn, N. Y.; Irvin J. Cohen, Brooklyn, N. Y.; Duncan S. Owen, Fayetteville, N. C.; Letcher E. Trent, Lexington, Ky.; M. M. Wassersweig, Reading, Pa.; Bryan N. Roberts, Hillsboro, N. C.; I. Dana Kahle, Knox, Pa.; W. J. B. Orr, Washington, D. C.; Robert W. Farr, Chestertown, Md.; Everet H. Wood, Auburn, N. Y.; Alvin E. W. Wode, Chevy Chase, Md.; George F. Sargent, Towson, Md.; R. B. Linger, Clarksburg, W. Va.; Douglas R. Dodge, Pasadena, Calif.; Harold H. Longwell, Tyrone, Pa.; J. Walter Layman, Hagerstown, Md.; Roger Brooke, Carlisle Barracks, Pa.; A. W. Valentine, Washington, D. C.; Clewell Howell, Towson, Md.; James McClung, Richwood, W. Va.; Seth H. Martin, Morrisville, Vt.; John W. Metcalf, Toronto, Ohio; Robert V. Palmer, Avenue, Md.; A. L. Lewis, Havre de Grace, Md.; Jack Sarnoff, Long Island City, N. Y.; John P. Keating, Forest Hills, N. Y.; John C. Hamrick, Shelby, N. C.; John R. Godbey, Charleston, W. Va.; O. T. McDonough, Jr., Washington, Pa.; J. Frank Williams, Jr., Clarksburg, W. Va.; F. T. Rogers, Ann Arbor, Mich.; L. C. Richmond, Milton, W. Va.; W. K. McGill, Clovis, S. C.; W. J. Heffner, Northport, N. D.; F. A. Carey, Taunton, Mass.; Elwood T. Quinn, Jenkintown, Pa.; George F. Leibensperger, Kutztown, Pa.; J. Henry Orff, Shillington, Pa.; Norman J. Wilson, Sparrows Point, Md.; Edward Baum, Philadelphia, Pa.; Frank W. Smith, Chestertown, Md.; Leo Brown, Washington, D. C.; E. P. Roop, New Market, Md.; L. E. Pulaski, Shenandoah, Pa.; J. D. Hoffman, Grove City, Pa.; G. Kirby Collier, Rochester, N. Y.; Albert E. Kovarsky, Perth Amboy, N. J.; Samuel Zeiger, Brooklyn, N. Y.; H. C. Bridgers, Blue Ridge Summit, Pa.; W. A. Bridges, Towson, Md.; Michael J. Egan, Savannah, Ga.; L. W. McGregor, St. George, Utah; W. F. Gemmill, York, Pa.; Louis H. Gale, Erie, Pa.; James A. Miller, Pikesville, Md.; H. W. Fancher, Enfield, Conn.; W. Millard Stirling, Fallston, Md.; Fred C. Steuart, Manchester, N. H.; Drs. Lee Cohen, J. King, B. E. Seegar, E. B. Freeman, Harry M. Robinson, Jr., E. H. Kloman, C. Reid Edwards, E. B. Friedenwald, J. Morris Reese, Thomas W. Keown, John R. Abercrombie, Howard M. Bubert, Monte Edwards, G. B. Mansdorfer, Milton Siscovick, N. E. Needle, Hugh R. Spencer, George H. Brouillet, C. Loring Joslin, Louis Diener, C. B. Ensor, Ralph Truitt, James G. Howell, Louis C. Dobihal, H. M. Robinson, Sr., J. Warren Albrittain, J. M. Hundley, Jr., Louis H. Douglass, J. Morley Hoag, Arthur Hebb, Harvey G. Beck, L. G. Llewelyn, E. P. Smith, John T. Hibbits, S. S. Glick, E. H. Tonolla, George McLean, John Evans, Edward A. Looper, C. W. G. Rohrer, A. E. Goldstein, C. G. Warner, Charles Bagley, Jr., George W. Murgatroyd, Howard Kahn, Edwin Plassnig, Hiram L. Rickard, and M. Paul Byerly of Baltimore.

ITEMS

Dr. Henry J. Walton, Professor of Roentgenology, was elected President of the American College of Radiology at the annual meeting held in New York City early in June.

A native of Genoa, Nebraska, Dr. Walton was graduated from the Baltimore Medical College in 1906. He studied further the next year at Berlin, Vienna, London and Paris, and practiced general surgery in Baltimore from 1907 to 1911.

In the latter year he was made assistant in roentgenology at the University of Maryland, a position he held until he succeeded the late Dr. Henry Chandlee as head of the department. From 1914 to 1916 Dr. Walton also was assistant in roentgenology at the Johns Hopkins Hospital.

Dr. Walton has been chairman of the Radiology Section of the Baltimore City Medical Society and the Southern Medical Association. He is chairman of the Baltimore Section of the Eastern Roentgenologists, who will meet here next year in annual convention.

Dr. Frank Tipton Rogers (U. of Md. 1935), instructor in the Department of Roentgenology, University Hospital, Ann Arbor, Michigan, has been certified as a specialist in radiology by the American Board of Radiology.

Dr. Eugene E. Covington, Associate in Gross Anatomy and Instructor in Surgery, participated in the program of the meeting of the Maryland Academy of Medicine and Surgery which was held on April 16, 1940. His subject was "Carcinoma of the Rectum, with Special Emphasis on the Present-Day Status of Irradiation Therapy."

Dr. Leonard J. Bowman (B.M.C. 1893) of Enderlin, North Dakota, plans to retire on March 30, 1943 after fifty years of active practice. He is one of a class of 142 students who received their medical degrees in 1893 and is looking forward to the fiftieth reunion of that class in 1943. Dr. Bowman is very anxious to hear from any of his classmates who may read this item and perhaps be interested to start planning for an enthusiastic reunion.

Dr. William H. F. Warthen, Assistant Professor of Hygiene and Public Health, has accepted the position of health commissioner of Baltimore County and will assume his new duties on August 1, 1940.

Dr. Francis A. Ellis, Assistant Professor of Dermatology, announces the removal of his office to 8 East Madison Street, Baltimore, Maryland.

Dr. S. Glenn Love (U. of Md. 1914) and Dr. Benjamin I. Siegel (Class of 1934) have been appointed senior surgeon and associate surgeon, respectively, on the Medical Staff of the new York County Hospital, Rock Hill, S. C., which has been approved by the American College of Surgeons and the American Hospital Association. Doctors Love and Siegel will continue to serve on the Medical Staff of the St. Philip Mercy Hospital, Rock Hill, S. C., in the same capacity.

OBITUARIES

WILLIAM TATE CAMERON, M.D.

Dr. William Tate Cameron, P. & S. 1889, aged 74, died in Mill Creek, West Virginia on April 12, 1940 of cerebral hemorrhage.

Dr. Cameron attended Virginia Military Institute at Lexington. He studied pharmacy at the Richmond School of Pharmacy, Richmond, and was a registered pharmacist.

Soon after receiving his medical degree Dr. Cameron began the practice of medicine in the rugged mountainous section of West Virginia in the vicinity of what is now Mace. He served the people of a vast territory, including parts of three counties, for over fifty years. At the beginning of the present century Dr. Cameron was very active, the country was thinly populated, and his only means of transportation was horseback or a buggy.

Dr. Cameron was a country physician who knew the human side of medicine. His sympathy, cheer and optimism were well known and appreciated by all who knew him as a patient or a friend. His death leaves a void in the lives of many.

JOHN M. ELDERDICE, M.D.

Dr. John M. Elderdice, U. of Md. 1905, aged 60, died in Salisbury, Maryland on April 10, 1940.

A practicing physician in Salisbury for twenty-seven years, Dr. Elderdice was a member of the Peninsula Hospital staff, the Wicomico County Medical Society and the American Medical Association. During the World War he served as a captain in the Medical Corps.

FRANCIS HOWARD FINLEY, M.D.

Dr. Francis Howard Finley, P. & S. 1895, died in Finleyville, Pennsylvania on December 24, 1939.

Dr. Finley was born in Finleyville on November 23, 1871, the son of Dr. F. M. and Emeline Thompson Finley. After graduation from the College of Physicians and Surgeons he took special courses in diseases of the chest, operative surgery, diagnosis and treatment of diseases of infants and children, and diseases of the ear, nose and throat. He seved as clinical assistant at the Hebrew and Baltimore City Hospitals, after which he returned to his home as a consultant.

During his college training Dr. Finley became closely associated with the late John J. McGraw, former manager of the New York Baseball Club, and for many years traveled with the club during its spring training season. In the winter of 1913–1914 he made a trip around the world with the New York Giants and the Chicago White Sox.

Dr. Finley was President of the First National Bank of Finleyville and a member of numerous sports and social clubs. He was very fond of the outdoors and bird life, and was noted for his warm hospitality and outstanding personality. His passing removes from Finleyville the last of the Finleys, a great loss to his many friends who knew his true worth.

WILLARD M. HILLEGEIST

Mr. Willard M. Hillegeist, Director of Admissions of the University of Maryland and an official of the institution for nearly thirty years, died on June 2, 1940.

A native of Baltimore, he attended Polytechnic Institute before attending the University, which was then known as the Maryland State College of Agriculture. Within a year after completing his scholastic work at College Park in 1912, Mr. Hillegeist returned to the University to act as secretary to Dr. H. J. Patterson, then president of the institution. With the exception of one year during the World War period, when he did special work for the United States Department of Agriculture, Mr. Hillegeist remained in the service of the University. In 1917 he became registrar of the College Park institution and in 1920, when the Maryland State College of Agriculture and the professional schools in Baltimore consolidated to establish a State University, he was named registrar of the University.

In 1935, when Dr. H. C. Byrd, then acting president of the University, put into effect his reorganization program, Mr. Hillegeist was promoted to the newly-created post of Director of Admissions.

He was former vice-president and treasurer and a member of the executive board of the American Association of Collegiate Registrars and he organized the Maryland Association of Collegiate Registrars, which later became the nucleus of the Middle States Association.

Word of Mr. Hillegeist's death was received with regret by the faculty and students of both the Baltimore and College Park branches of the University, where he was known as "Hilley".

In speaking about Mr. Hillegeist, a recent issue of one of the University's student annuals remarked, "That feeling of being at home, which supplants that sense of utter helplessness experienced by every freshman entering college, is due to the merry smile, wholesome handshake, and the sincere words of greeting accorded by our Director of Admissions."

Mr. Hillegeist was the kind of sincere friend that everyone wants to keep. He was not only admired but respected. At all times he seemed jolly, smiling as if for the pure pleasure of being happy. He took a sincere and active interest in our problems, our families, our aspirations and ambitions. Truly, he was a creative and patient listener. One might say that "Hilley" was lighthearted, yet he was serious when the occasion arose, always master of his worries. His associates will miss a staunch, genial and loyal friend.

Willard M. Hillegeist

WILLIAM S. LOVE, SR., M.D.

Dr. William S. Love, Sr., whose grandfather and great-grandfather were physicians and whose only son is a member of the faculty of this University, died at Bon Secours Hospital on May 13, 1940, at the age of seventy-three. He celebrated the fiftieth anniversary of his work as a physician during his last illness, which was of one month's duration.

Dr. Love graduated from the Maryland State Normal School in 1887, and from the University of Maryland School of Medicine in 1890. He took great interest in the alumni activities of these institutions and was a former president of both Alumni Associations.

He taught at the Woman's Medical College and at the Maryland Medical College. At the latter institution he held the Chairs of Gastro-enterology, and later of Materia Medica and Therapeutics. He helped to found the West Baltimore Medical Association, which has since become the Maryland Academy of Medical and Surgical Sciences, and was its treasurer at the time of his death. He was a fellow of the American Medical Association, and a member of the Baltimore City Medical Society and the Medical and Chirurgical Faculty of Maryland.

Dr. Love was outstanding in his strong desire to maintain and uphold the high level of medical ethics obtaining at the time he began to practice. He deplored any trend toward the commercialism or newer systems of practice that would conflict with the close personal relationship between physician and patient. He considered specializing at many times but preferred the human association with his patients in a large general practice. He was not only physician to many, but also father-confessor and adviser. He was fortunate to have lived long enough to bring, in many instances, three generations of the same family into the world. His friends, colleagues and patients will miss a man of strong character, kindly demeanor and true value, a man who was admired by all faiths and creeds.

THOMAS M. TALBOTT, M.D.

Dr. Thomas M. Talbott (U. of Md. 1870) died at his home in the village of East Falls Church, Virginia on May 4, 1940 at the age of ninety-one.

Dr. Talbott was born near White's Ferry in Montgomery County, Maryland in 1848. He attended public school at Poolesville, Maryland, and graduated from the old Columbian College, now George Washington University, before studying medicine at the University of Maryland.

In the early days of his practice Dr. Talbott traveled on horseback and carried his surgical instruments and medicines in saddle bags. Later he used a horse and buggy. More than 2,000 present and former residents of Fairfax and Arlington Counties gave their first cries at birth in the gentle hands of the practitioner, who liked best to describe himself as a "horse and buggy" doctor.

He treated a multitude of ailments and rendered service in many epidemics, always keeping abreast of progress. In 1880 he installed the first telephone in Virginia. Still he traveled by horseback, his saddle bags filled with the materials for the pills he rolled in corn meal, mixing them according to his own prescriptions. Later he invested in a sulky, and finally he bought one of the first automobiles seen in his community.

Many of his patients and friends accompanied him on his last trip through the northern Virginia country to his final resting place. They will miss a gentle physician, loyal friend and kindly adviser.

Bennett, John Henry, York, Pa.; class of 1892; served during the World War; aged 67; died, January 4, 1940.

Black, Thomas F., Providence, R. I.; P. & S., class of 1890; aged 76; died, April 2, 1940, of arteriosclerosis and heart disease.

Brigham, Frederick Clayton, Springfield, Mass.; B.M.C., class of 1898; aged 68; died, January 22, 1940, in the Westfield (Mass.) State Sanatorium of pulmonary tuberculosis.

Brown, Tennant Bledsoe, Columbia, Tenn.; B.M.C., class of 1897; aged 66; died, March 4, 1940, of pneumonia.

Burruss, Charles Overton, Sharon, S. C.; class of 1906; aged 58; died, February 27, 1940, in the Mercy Hospital, Charlotte, N. C. of essential hypertension, arteriosclerosis and cerebral hemorrhage.

Campbell, James Wallace, Gastonia, N. C.; P. & S., class of 1893; aged 69; died, March 20, 1940, of carcinoma of the liver.

Cassidy, Henry Francis, Baltimore, Md.; class of 1890; aged 70; died, February 12, 1940.

Cloonan, John Joseph, Stamford, Conn.; P. & S., class of 1897; aged 69; died, January 28, 1940, of cardiovascular renal disease.

Dixon, William Francis, Carbondale, Pa.; P. & S., class of 1902; aged 63; died, February 11, 1940, of duodenal ulcer.

Finley, Joseph Lane, Grasonville, Md.; class of 1884; aged 79; died, February 18, 1940, of arteriosclerosis.

Gatsos, Peter Nicholas, Cleveland, Ohio; class of 1916; aged 57; died, February 7, 1940, of coronary thrombosis.

Hacker, Chauncey C., Elizabethton, Tenn.; P. & S., class of 1907; formerly Mayor; aged 63; died, January 14, 1940, of coronary thrombosis and arteriosclerosis.

Halsey, Hugh, Montclair, N. J.; P. & S., class of 1886; aged 75; died, March 21, 1940, of heart disease, arthritis and arteriosclerosis.

Hanes, John Lewis, Pine Hall, N. C.; class of 1902; aged 60; died, January 15, 1940, of lobar pneumonia.

Hankey, Elmer Howard, Pittsburgh, Pa.; P. & S., class of 1914; aged 51; died, in March, 1940, of cirrhosis of the liver.

Hennesey, James F., Stamford, Conn.; class of 1904; aged 63; died, April 11, 1940, after a lingering illness.

Houghtaling, Frederick Morell, Sandusky, Ohio; B.M.C., class of 1896; served during the World War; aged 66; died, April 17, 1940, of cerebral hemorrhage.

Johnson, William Henry, Turlock, Calif.; B.M.C., class of 1904; aged 67; died, December 28, 1939.

Lightner, Theodore, Hastings, Nebr.; class of 1880; aged 83; died, January 18, 1940, of myocarditis.

McCaleb, Jonathon Howard, New Orleans, La.; P. & S., class of 1881; aged 84; died, January 7, 1940.

McKenna, Frank A., Pawtucket, R. I.; P. & S., class of 1894; aged 73; died, March 3, 1940, of chronic arthritis and myocarditis.

Manley, Peter Charles, Scranton, Pa.; P. & S., class of 1881; aged 82; died, February 24, 1940, of arteriosclerosis.

Marsh, William A., Green Lawn, W. Va.; P. & S., class of 1904; aged 79; died, April 17, 1940, of cerebral hemorrhage.

Miller, John Peter, Grand Forks, N. Dak.; B.M.C., class of 1906; served during the World War; aged 60; died, April 18, 1940, of coronary thrombosis.

Miller, Joseph M., Charles Town, W. Va.; P. & S., class of 1877; aged 86; died, February 28, 1940, of senility.

Mitchell, Wayland, Lewiston, N. C.; class of 1895; aged 68; died, January 1, 1940, of myocarditis.

Quigley, John M., Clearfield, Pa.; B.M.C., class of 1898; aged 65; died, March 17, 1940.

Ray, Charles Andrew, Charleston, W. Va., P. & S., class of 1887; aged 75; Medical Director of the Kanawha Valley Hospital; died, January 21, 1940.

Ridgeway, Fountain Burr, Buckhannon, W. Va.; P. & S., class of 1891; aged 73; died, in January, 1940, of diabetes mellitus.

Rosett, Joshua, New York, N. Y.; class of 1903; aged 64; died, April 4, 1940, in Merida, Yucatan, Mexico, of carcinoma of the stomach.

Shannon, George Conkley, Baltimore, Md.; B.M.C., class of 1883; aged 75; died, February 13, 1940, of pneumonia.

Sorenson, Anton Christian, York, Pa.; P. & S., class of 1911; served during the World War; aged 71; died, February 26, 1940, of cirrhosis of the liver.

Spangler, Charles C., York, Pa.; P. & S., class of 1915; served during the World War; aged 53; died, January 17, 1940.

Stevens, Martin L., Ashville, N. C.; B.M.C., class of 1891; aged 75; died, January 20, 1940, of coronary thrombosis.

Sutton, Edward L., Bellevue, Pa.; class of 1907; aged 60; died, January 25, 1940, of influenza and pneumonia.

Thompson, Charles Author, Newton, Mass.; P. & S., class of 1896; aged 67; died, February 3, 1940, of cerebral hemorrhage and arteriosclerosis.

Trippe, Samuel C., Royal Oak, Md.; class of 1875; aged 90; died, January 24, 1940, in the Emergency Hospital, Easton, of a hip fracture received in a fall.

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PROGRESS IN THE KNOWLEDGE AND CONTROL OF CANCER*†

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BALTIMORE, MD.

During the past twenty-five years cancer has become a public health problem of the first magnitude. The extent of the problem becomes apparent when it is considered that in the United States during the past year approximately 156,000 persons have died of this disease.

Cancer is now second on the list as a cause of death; twenty-five years ago it ranked seventh. Dublin (5) has estimated that in the United States, by 1960, with a total population of 147,000,000 there will be approximately 56,000,000 who will have reached or passed their forty-fifth year and that the annual number of deaths from cancer will approximate 270,000. Triumphs in preventive medicine and advances in the treatment of certain diseases are in a large measure responsible for this apparent increase in cancer. In 1900 the expectancy of life was approximately forty years—and one person in twenty was over sixty years of age. Today life expectancy is about sixty-four years and one person in twelve is over sixty years of age. Simply stated it is the matter of more persons reaching the "cancer age".

Although cancer is as old as the race, definite knowledge of its morphology has been gained only during the past hundred years. Cooperative studies by clinicians and pathologists have shown that there are many distinct types of cancer. These types vary much in structure, in rate of growth, in the formation of metastases, and in response to irradiation.

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* From the Department of Pathology, School of Medicine, University of Maryland.

† Read before the Allegany-Garrett Counties Medical Society, May 24, 1940.

The histologic study of human cancer has shown that the lack of cell differentiation is often associated with rapid growth and that the degree of differentiation may in a measure serve as an index of irradiation effect. It has also demonstrated that neither bacteria nor any other visible form of life may be for the present accepted as a universal cause of the disease. Moreover, studies of the cells in cancer have shown that, unless the macronucleolus idea of MacCarty be accepted, there is no morphologic basis for the recognition of a cancer cell as such. Rather is a malignant tumor recognized on the basis of the behavior of its cells in relationship to those of the surrounding tissue.

Normal cells multiply, differentiate and form organized tissue. These potencies are controlled. Cancer cells multiply and in this they are autonomous, they do not completely differentiate nor do they organize.

It is held that completely differentiated, highly specialized cells do not divide; hence cancer must arise from incompletely differentiated cells which Reimann (11) has designated as "spare parts". These cells have several potencies and respond to various stimuli in different ways. Thus, to functional demand the response may be hyperplasia and regeneration; or the response may be metaplasia such as is seen in the mucosa of the trachea in vitamin A deficiency, where in regeneration the cylindric epithelium may be replaced by squamous cells, or in the change from cylindric epithelium to squamous epithelium in the prostate following estrin administration. Finally, all incompletely differentiated cells have the potency of developing tumors if exposed to the proper stimuli.

Cancer cells multiply more slowly than do cells of normal tissues. The rapidity of growth of granulation tissue is a good comparative example. Whipple has shown that in dogs as much as 200 grams of liver tissue may be regenerated within two weeks. Tumors do not grow that rapidly. The important manifestation of cancer is, therefore, not the rapid multiplication of its cells but rather the inability of these cells to completely differentiate and to organize.

Experimental homologous transplantation of tumors in animals has shown that the growth which develops in the new host arises from the cells that have been introduced and that the cells of the host take no part in tumor production. Moreover, the study of human material shows that cancer cells and normal cells in the same environment behave differently and that the biological character of the normal cells is not changed by such exposure. The property of malignancy thus appears to be an inherent potentiality of the cancer cell. It is a fixed characteristic which persists in successive transplantations and in widespread metastases.

Little (10), in discussing the development of tumors in mice, suggests that the process of carcinogenesis is one in which there are three variables: (1) "Some physiologic unbalance or irritation caused by hypo- or hyperfunction of tissues or experimentally introduced by the application of chemical or physical agents for that purpose." (2) "Internal environmental conditions such as sex, physiologic age, etc." (3) "The genetic constitution of the tissue affected." As applied to human cancer these variables may be considered under the headings of extrinsic and intrinsic factors. (It is to be understood that the former applies to all influences originating outside of the cell and that the latter refers to properties or potentialities of the cell itself.) Boyd (3) offers the following simile: "In the case of a fire the extrinsic factor is the match, the intrinsic factor is the inflammable nature of the material. Both are needed before the fire will start." The extrinsic factors responsible for cancer of the cervix, cancer of the liver and cancer of the breast are almost certainly not the same, although the intrinsic factor may be identical in all.

The occurrence of occupational cancer and the association of this disease with chronic infections have long been recognized. Cancer of the bladder in aniline dye workers, cancer of the lip in fishermen who repair tarred nets, cancer of the skin in radium and roentgen ray workers, cancer of the lung in Schneeberg miners, and cancer of the bone in watch dial painters are well-known examples of the occupational types. Cancers in relation to syphilis of the tongue, tuberculosis of the skin, and parasitic infestation of the liver may be mentioned as examples of types associated with chronic infection. These and other leads have served to focus attention to chronic irritation as an important extrinsic factor in cancer.

The earliest experimental work along these lines was that carried out by Fibiger, who produced tumors in the stomach of rats by causing invasion of the stomach wall by nematodes. In 1916 two Japanese pathologists were able to produce cancer on the skin of rabbits through repeated paintings with tar. It was then thought that simple chronic irritation was the inciting factor. Careful studies have subsequently shown that the low boiling point, highly irritating fraction of tar is impotent in producing cancer and the high boiling point, less irritating fraction is carcinogenic.

Kennaway and Cook, in studying the various compounds of tar, have isolated the active carcinogenic hydrocarbons 1–2–5–6 dibenzanthracene and 3–4 benzpyrine. With these compounds many types of cancer have been produced in experimental animals. The results of these experiments have shown that the activity of the inciter does not depend upon simple irritation, that the inciter acts as an original stimulus, and that its continuous presence is not required since cancer may develop many months after its withdrawal.

For some time it has been known that a relationship exists between certain tumors and the endocrine glands. Thus, in embryonal carcinoma of the testicle and in choriocarcinoma the anterior lobe of the hypophysis is stimulated to produce excessive quantities of prolan A, a substance which normally induces ripening of the follicles in the ovary. In the case of these tumors the hormone appears in the urine and may be recognized by the Friedman test.

It is well known that the estrogenic hormones stimulate the development of the female breast at the time of puberty. Recently it has been shown that these substances are capable of producing carcinoma in the mammary glands of mice. Cramer (4) cites experiments on mice to indicate that the cortical hormone of the adrenal is essential for the full development of the action of estrogens, and that the hormones of the anterior lobe of the pituitary and of the medulla of the adrenal are antagonistic, thus suggesting an endocrine imbalance as the basis for the production of cancer of the mammary glands in these animals. This conception of endocrine imbalance might be kept in mind as a useful guide for clinical investigation in the matter of cancer of the breast in women.

Definite proof that estrogens produce tumors in the human has not been established, although it is known that these hormones will produce hyperplasia of the epithelium of the breast and in the glands of the uterus. Allaben and Owen (1) report the case of a fifty year old woman who during the period of a year received 258,000 units of theelin. Six months after the termination of this treatment a carcinoma was removed from her right breast. These authors do not commit themselves upon the relation of the treatment to the appearance of the tumor. Auchincloss and Haagensen (2) report a case of cancer of the breast in a woman who gave a history of breast cancer in her immediate family. This patient, because of menopausal disturbances, had received considerable amounts of estrogens over a period of two years and nine months. Her breasts had been carefully examined during the first two years and no lesions were found. Toward the end of the third year two lumps were discovered in the breast; one was a cyst and the other was a carcinoma which had metastasized to the axillary nodes.

These cases are not cited in an effort to prove that estrogens cause cancer in humans. The purpose is rather to sound a note of warning against the indiscriminate use of these hormones and to call attention to the importance of frequent checkups in the matter of the breasts and uterus in women who have been so treated. It is interesting to note that there is a close chemical relationship between the estrogens and the carcinogenic agents obtained from tar.

A word might be said with regard to viruses as an extrinsic factor in the production of tumors. The available information deals with neoplasms in animals. Rous has shown that fowl sarcomas are transmissible by a cell-free filtrate. Lucke has described a kidney tumor in frogs that can be transmitted in the same way. The only known association between a virus and a malignant mammalian tumor is that cancer may develop in a virus-produced papilloma. The Shope virus obtained from papillomas in cottontail rabbits produces a much more active growth in domestic rabbits. The lesions in these animals become fissured and ulcerated, and frequently lead to low grade carcinoma. Rous combined the action of benzpyrine and rabbit papilloma virus by rubbing the chemical upon the skin of the rabbit and injecting the cell-free filtrate into the blood stream. Tumors produced by this method were more vigorous than after the action of either agent alone, and, moreover, many of the papillomas became malignant.

These experiments suggest again that multiple extrinsic factors may be responsible for the production of some cancers and that a virus may be one of the agents. There is no definite information on the relationship of viruses to tumors in the human.

The identification of the intrinsic factors in carcinogenesis is exceedingly difficult. The most tangible and thus the most important intrinsic factor in experimental cancer is heredity. Slye, by selective breeding, has produced strains of mice in which almost 100 per cent develop spontaneous cancer. She has also produced strains that are highly resistant to the development of spontaneous tumors. Inherited susceptibility seems to reside principally in cells of a particular organ, depending upon the particular strain of mouse. Thus it has been possible to produce a group of mice that consistently develops carcinoma of the mammary gland, another that will develop carcinoma of the lung, and still another that develops carcinoma of the liver. In some of these experiments it has been possible to predict the age at which the tumor will make its appearance.

It is difficult to know to what extent these results can be applied to man. Little is known about the nature of the diseases that have killed our forebears and for the present, at least, breeding in humans is not controllable. The occurrence of cancer of a particular organ in members of the same family group at approximately the same period of life is well established. The development of the same type of tumor in the same organ in identical twins has been rather frequently noted. From this standpoint it may be said that occasional tumors or tumors of different types in a family are not significant, but that the frequent occurrence of a particular type in a particular organ points strongly to an inherited susceptibility. Persons in whom this susceptibility may be expected should be subjected to thorough physical examinations through the age period when such tumors are expected to develop.

Elsewhere in this paper reference has been made to the relationship between cancer cell differentiation and the degree of malignancy. It is well known that the cells of some carcinomas of the cervix may in general resemble closely the squamous epithelium from which they have originated. In other cervical carcinomas the cells may have no morphological resemblance to squamous epithelium. In the first group it has been observed that the tumors grow more slowly, invade less actively, and metastasize at a later period. Those of the second group are characterized by rapid growth, extensive invasion, and early metastases. As a result of these and similar observations, pathologists following the lead of Broders are attempting to grade tumors on a histologic basis.

There can be no doubt but that the more undifferentiated cells there are in a tumor, the more rapid the growth, the greater chance for spread, and the less opportunity for complete removal or destruction of the tumor. However, to attempt to determine the prognosis in any given case of malignancy on the basis of the histologic study of the tumor alone is likely to be disappointing.

Other important factors are to be considered. It is well to remember that breast cancer in a woman under thirty will generally behave in a manner quite different from the same type of cancer in a woman of sixty-five. The most important factor in determining the ultimate outcome in cancer is the extent of growth. A grade I tumor which has metastasized to the liver, lungs or bone will prove fatal just as certainly as a grade IV tumor that has similarly metastasized.

Intimately associated with attempts at grading are efforts to predict the effects of roentgen rays and radium upon the tumor cells. It is known that embryonal tumors of the testicle and ovary are highly sensitive to irradiation and that, in general, tumors composed of poorly differentiated cells exhibit poor resistance when exposed to roentgen rays or radium.

Factors other than the degree of cell differentiation operate in the determination of response to irradiation. Certain tissues exhibit inherent qualities of radio resistance or of radio sensitivity. Nerve tissue is inherently resistant and it is therefore not surprising to note that nerve tumors, among them neurogenic sarcoma, are generally resistant. However, while lymphoid tissue is relatively resistant, yet lymphosarcomas composed of relatively well-differentiated lymphocytes are among the most sensitive of tumors. Tumors that excite a desmoplastic reaction (fibrosis) in the host are resistant. Fat similarly constitutes an unfavorable bed for the irradiation of tumors. This has a bearing on the practical treatment of cancer in a fatty breast. Prior treatment of sensitive tumors by irradiation followed by tumor regeneration usually results in radioresistance. Radiosensitivity is not to be confused with cure by irradiation.

Little has been added in recent years to the armamentarium of the pathologist in the matter of recognizing malignancy. No satisfactory test has been devised thus far. The clinical diagnosis of cancer still depends on the finding of a "lump," an ulcer, or an obstructing or bleeding lesion. Gross and microscopic examinations of the tissue by a competent pathologist still yield the most accurate information as to the character of a growth. Ewing (7) very clearly defined the object of a biopsy when he said that the purpose of this procedure is to make a diagnosis promptly, positively, and with as little harm to the patient as possible. The pathologist is not infrequently put at a disadvantage because the tissue removed is either insufficient or not representative. Moreover, surgeons sometimes forget that the location, size, duration and general physical characteristics of a tumor often form the background for pathologic diagnosis. A knowledge of the clinical history is often highly essential in the matter of differential diagnosis. This applies particularly to lesions of the lymph nodes.

There has been much discussion as to the proper method of removing tissue for diagnosis. Some surgeons prefer to cut directly into the lesion on the basis that the blood flow is toward the incision and that there is less likelihood of the tumor cells being sucked back into the blood vessels. Others, where possible, excise the lesion with a good margin. By the latter method there is less opportunity to scatter tumor cells into the surrounding area and if the tissue is handled gently the chance of forcing cells into the blood vessels does not appear to be great. Certainly the danger of dissemination seems less than that occasioned by the frequent and forceful palpation to which some breast cancers are subject.

The method of aspirating tumors for diagnosis has been used for some time. It has been recently popularized by the group at the Memorial Hospital in New York City. The technique commonly used employs a 20 cc. tight syringe fitted with an 18 bore needle. The skin is sterilized and anesthetized, and the needle pushed into the tumor. Suction usually forces material into the needle. This is pressed out on a slide and stained. The advantages of this method lie in the fact that it saves time and is not disturbing to the patient. The disadvantages are that the aspiration may not withdraw characteristic tissue or coherent masses of cells, and that correct interpretation depends upon wide experience. The method is suited to clinics with a large quantity of tumor material. It should not be used as an occasional procedure by those untrained in the method.

Finally, the outlook for cancer is not hopeless. Slowly but surely fundamental facts concerning the nature and treatment of the disease are being brought to light. Never before has cancer research offered so many alluring leads. There is the eternal hope that the causes of this dread malady may be unveiled. Great advances in the treatment of cancer by means of supervoltage roentgen ray machines are anticipated. Studies of the effect of refrigeration are being made. Proper education of the public is still highly necessary. Fear is a lesser evil than cancer for, as someone has said, "Cancerophobia does not metastasize nor does it kill." The physician must become cancer-minded and thus constantly be on the alert for early signs of the disease.

Nearly 2000 years ago Celsus wrote, "Only the beginning of a cancer admits of a cure; but when 'tis once settled and confirmed, 'tis incurable and the patient must die under a cold sweat." How true this is even today!

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CANCER OF THE CERVIX*†

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This paper is a résumé of the symptoms, pathology, present-day opinions of irradiation therapy, and results of radium and roentgen therapy for carcinoma of the cervix. It was not written for the expert in oncology, but for the general practitioner. From it he may obtain a practical working knowledge of the subject without having to learn too many technical factors of physics and allied subjects, as seen in current radiological literature.

INCIDENCE

There are approximately 15,000 deaths annually in the United States from cancer of the uterus. The State of Maryland has an annual death rate of about 250 from this disease. Cancer of the uterus is the second most common of all types of malignancy; cancer of the stomach is first with an annual death rate of nearly 25,000, a high percentage of which is in men; and cancer of the breast is third in order of frequency with an annual death rate of approximately 12,000.

ETIOLOGY

The actual cause of cancer of the cervix is unknown; however, there are several contributing factors which are well known. Chronic irritations, such as endocervicitis, erosions, unrepaired tears from childbirth, and the excessive use of strong chemicals as douches are etiological factors in cancer of the cervix. Graves (1) has shown conclusively the difference in incidence of this type of malignancy in women who had routine cervical repair compared with a series of cases without routine postpartum repair of the cervix. The cancer rate was several times higher in the cases without routine postpartum repair. The general practitioners and obstetricians of this country could probably reduce the death rate from this type of cancer by the repair of every cervix following delivery.

Recent studies indicate that the excessive action of ovarian hormones is a factor in the etiology of cancer of the cervix. The studies were based on the experimental injection of animals with larger than normal quantities of hormones. The evidence is fairly conclusive in animals, but it is too early yet to say that hormonal stimulation is the

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cause of cancer in humans. In the reports on breast tumors now appearing in the literature most authors believe the cancer was caused by prolonged treatment or excessive doses of estrogenic hormone.

GROSS PATHOLOGY

There are two distinct types of gross pathology in cancer of the cervix, the everting and the inverting types. On bimanual examination the everting type feels like a cauliflower mass projecting from the cervix. It has a tendency to grow downward toward the vagina and not laterally toward the parametrium. The uterus is freely mobile as long as the lesion is still early. Examination of the inverting type usually reveals the cervix destroyed by tumor, except possibly its outer rim, and thus it gives the impression of a crater-like ulcer. Any combination of these two types of gross pathology may be present. The pathology is important because the inverting type extends laterally toward the parametrium and pelvic lymph nodes earlier. Pressure on the ureters is more common, and infections are more often present than with the cauliflower growths; therefore, the ultimate prognosis of the everting type is usually much better.

MICROSCOPIC PATHOLOGY

About 5 per cent of all cancers of the cervix are adenocarcinomas, while the remaining 95 per cent are squamous cell cancers. Microscopic grading should always be done, although its value has never been thoroughly established. Rankin and Broders (2) have shown its value in the prognosis of cancer of the rectum. Sometimes a biopsy will show a grade III malignancy, and a biopsy 2 cm. distant from the same tumor, taken at the same time and interpreted by the same pathologist, will show grade II or grade IV malignancy. A biopsy from the same location two weeks later and interpreted by the same pathologist may shown an even different grade of malignancy. This would sound as if microscopic grading might be unreliable; but the author believes with Broders of the Mayo Clinic that, granting there may be variations and discrepancies, if studied carefully long enough it will be of value in prognosis. It certainly seems reasonable to think that, other factors being equal, a rapidly growing (grade IV) tumor has a less favorable prognosis than a slowly growing (grade I) tumor. A résumé of the literature on microscopic grading of cancer of the cervix from practically all the large cancer clinics shows the average percentage of tumors in each grade as follows:

5 to 10 per cent of squamous cell cancers of the cervix are grade I
10 to 15 per cent of squamous cell cancers of the cervix are grade II
25 to 30 per cent of squamous cell cancers of the cervix are grade III
40 to 50 per cent of squamous cell cancers of the cervix are grade IV

For practical purposes one-half to three-fourths of all cervix cancers are, microscopically, rapidly growing (grade III or IV) tumors.

CLINICAL PATHOLOGY

The clinical pathology, or the various successive stages of the gross pathology, is far more important in prognosis than microscopic grading. The League of Nations and nearly all cancer clinics throughout the world have adopted the following clinical stages:

Stage I—Disease limited to the cervix, uterus freely mobile.
Stage II—Disease of the cervix spreading into vaginal fornices, uterus still mobile.
Stage III—Disease of the cervix spreading to the parametria and pelvic lymph nodes, uterus partially mobile.
Stage IV—Disease of the cervix with extensive involvement of both parametria, involvement of the bladder or rectum, or distant metastases, i.e., liver, lungs or bone.

The following various clinical stages of the gross pathology are revealed on examination:

5 to 10 per cent of all cancers of the cervix are stage I
15 to 25 per cent of all cancers of the cervix are stage II
40 to 50 per cent of all cancers of the cervix are stage III
15 to 25 per cent of all cancers of the cervix are stage IV

For practical purposes one-half to three-fourths of all cancers of the cervix are clinically late (stage III or even IV) when first seen. Taking this fact into consideration, and also the fact pointed out in a preceding paragraph that one-half to three-fourths of all cases have microscopically highly malignant (grade III or IV) cells, it is no wonder that the ultimate prognosis of cancer of the cervix is so unfavorable.

AGE

There is no definite age for cancer of the cervix, but 75 per cent of all cases are between thirty-five to fifty-five years of age. Age is a factor in prognosis. Young individuals do not get along as well as older women with cervix cancer. The author has had three cases of cancer of the cervix in women below thirty years of age in the past two years. In these cases the disease progressed rapidly. The Memorial Hospital of New York City has no record of a cured case by any method of therapy in a woman below thirty years of age.

SYMPTOMS

There are three classical symptoms of cancer of the cervix: (1) Bleeding, either menorrhagia, metrorrhagia, or occasionally frank hemorrhage, is the first symptom in approximately 75 per cent of all cases. The cauliflower growth bleeds earlier, as a rule, than the inverting type. This fact is a definite factor in prognosis because women will usually consult the physician for abnormal bleeding and thus they get treatment earlier. (2) Discharge, usually a foul-smelling watery leukorrhea associated with tumor necrosis and secondary infection, is the first symptom in about 20 to 25 per cent of these cancers. The author believes this symptom is most often seen in the inverting type of cancer. (3) Pain is the first symptom in only about 5 to 10 per cent of all cases. It is a late symptom and means involvement of the parametria, pressure on the ureters, or involvement of the bladder and rectum.

RADIOTHERAPY

The present-day treatment for cancer of the cervix is irradiation, either radium alone or preferably radium and roentgen therapy combined. Radium alone is at present used in smaller hospitals or where roentgenotherapy is not available.

Roentgenotherapy is used, and preferably before radium therapy, for the following five reasons: (1) It helps to clear up the secondary infection. Douches are also important for the same purpose. Infection is most often seen in the inverting type growth. Clearing up the infection by roentgenotherapy makes radium treatment safer. (2) It reduces the size of the growth and thus lessens the amount of work for the radium. (3) It stops the bleeding by reducing the size and vascularity of the growth. (4) Roentgenotherapy without radium is used as a palliative agent for most advanced (stage IV) cases. The object here is to reduce the pain, decrease the size of the growth, stop bleeding and discharge, and in this way try to improve the general condition of the patient. Roentgen therapy has proved to be as good or even a better palliative agent than radium in these advanced cases, and with fewer complications. (5) It increases the amount of irradiation to the parametria and pelvic lymph nodes. This is by far the most important function of roentgen therapy. Radium alone will accomplish almost as well any of the other four reasons mentioned for its use. As a rule, early cancer of the cervix (stage I or II) is not fatal, but the mortality is high in late cancer (stages III and IV); therefore, the mortality is in direct proportion to the amount of extension into the parametria and pelvic lymph nodes. Roentgenotherapy has probably been the chief factor in the increase of the five year survival rate of cervix cancers, especially the improvement in the stage III group of cases.

Methods of roentgen therapy. There are two methods of giving roentgen therapy: (1) the massive dose technic popularized by Wintz, and (2) the fractional dose technic popularized by Coutard and Pfahler. Wintz (3) of Germany gives all the irradiation, six to eight portals directed to the cervix, at the first visit. Six weeks later another massive dose, eight to ten portals directed to the parametria, is given at one visit. Complications from this technic are too common. George Pfahler's saturation technic is not popular with most radiologists. His idea is to give a large amount of irradiation during the first few days of therapy, then add smaller amounts daily to keep up the saturation for three to five weeks. The Coutard principle of therapy is the most popular and has probably given the best results of any type of roentgen therapy. By Coutard technic is meant a low intensity (2 to 5 milliamperes), high voltage (200 kilovolts or more), divided dose (daily or originally twice daily), and a prolonged (three to five weeks) type of treatment. Very few clinics now use the low intensity (2 to 5 milliamperes) originally advocated by Coutard. They use a higher intensity (20 to 30 milliamperes) on account of the timesaving feature and because it is doubtful if there is any difference in the biological effect on the cancer cell. The prolonged divided dose technic has several advantages: (1) It saves the skin from overirradiation. (2) Larger doses can be given safely. (3) More cells are irradiated during mitosis, i.e., during their most radiosensitive stage. (4) Complications from overirradiation (radionecrosis, burns, etc.) are less common.

Author's technic of roentgenotherapy. The roentgenotherapy technic used by the author is a modified Coutard technic. It is fairly typical of that used by nearly all American, English and French clinics. A 200 kv. Keleket roentgen ray apparatus is used; 50 cm. distance; 1 mm. copper and 1 mm. aluminum filter; 4 or 6 field (12 x 12 cm.) technic. Two fields are treated daily, each receiving 1700 to 2000 roentgen units, or a total of 6000 to 8000 roentgen units over a period of three to four weeks.

Supervoltage roentgen ray. Supervoltage (200 to 1000 kv.) roentgenotherapy is now being used in several large clinics. Its value is not yet established because there are not enough statistics on five-year survivals to show its superiority over the customary 200 kv. roentgen ray apparatus used today. The literature on supervoltage roentgenotherapy shows the following: (1) There is a definite increase in the amount of irradiation reaching the parametrium and the pelvic lymph nodes. If all other factors are equal, this should give an increase in the five-year survival rate. It is too early to draw conclusions, but nearly all radiologists to date show better results with supervoltage therapy. (2) The irradiation reaction on the skin is less than with 200 kv. therapy. (3) The irradiation reaction to the deep structures, i.e., the vagina, rectum, and bladder, is much greater than with 200 kv. therapy. The cost of supervoltage apparatus is so high that it is impractical for the average radiotherapist or hospital. At the present time a radiotherapeutist can so increase the depth dosage with the ordinary 200 kv. roentgen ray apparatus by altering the other physical factors, such as distance, filters, and size of fields that, unless a definite biological difference can be noted from supervoltage therapy, only research institutions should spend the money for this form of therapy.

Intravaginal roentgen therapy. Within recent years intravaginal roentgenotherapy has been used by a number of clinics. It has two objects, to replace radium which is expensive and usually means hospitalization for treatment, and to increase the amount of irradiation in the parametrium and pelvic lymph nodes with less complications to the bladder and rectum. There is no literature at present that shows any increase in five-year survivals by this method. It has the serious disadvantage that, because of variations in anatomy caused by cancer invading the vaginal wall, parametrium or bladder, it can be used in only a few selected cases. It has no economic advantage over radium either for the patient or radiotherapeutist. The most recent work on the physical measurements of pervaginal roentgenotherapy was done by Morrison (4) of Canada. He compared the measurements with radium. His conclusions were that pervaginal roentgenotherapy gave more irradiation into the parametrium than radium alone applied in the cervical canal, but not as much as radium used by means of the colpostat technic. There was less irradiation to the bladder and rectum by intravaginal roentgenotherapy than with radium either in the cervical canal or by colpostat technic.

Radium therapy. Radium therapy is much older than roentgenotherapy. It is the most valuable single agent in the cure of cancer of the cervix. There are four different accepted technics of radium therapy: (1) The massive dose technic, which is advocated in this country by such eminent leaders as Healy (5), Burnam (6), and many others. Usually a heavy course of roentgenotherapy is given and followed in approximately two weeks by one large dose (3000 to 4500 mg. hrs.) of radium. (2) The continuous dose technic was originated by Claude Regaud (7) of Paris. A small quantity of radium (20 to 30 mg.) is used over a long period of time (five to twelve days). Regaud uses a colpostat technic.* (3) The divided dose technic was popularized by Heyman (8) of Radiumhemmet, Stockholm, and Bowing and Fricke (9) of the Mayo Clinic. Heyman gives three treatments spaced over a period of four weeks. He uses a heavy filter (3 mm. lead). The total dose is usually 2400 mg. hrs. in the uterine canal, and 4800 mg. hrs. in the vagina. The author uses a modified Heyman divided dose technic of radium therapy. (4) Interstitial implantation of radium for cancer of the cervix may be either intra-abdominal or pervaginal. Intra-abdominal implantation of radium has never been a popular method because it means an operation and hospitalization. Kidd (10), Gellhorn (11), Taussig (12), and many others have used this form of therapy. Pervaginal interstitial implantation is a fairly common form of radium therapy. It has been used in this country by such leaders as Pomeroy (13), Ward-Farrar (14), Martin (15), Pitts and Waterman (16), and Arneson (17).

Every physician should be acquainted with the inverse square law in the physics of irradiation. Irradiation loses strength inversely as the square of the distance from its source of origin. For instance, if 1600 mg. hrs. are given at a distance of 4 cm. from its source (the cervical canal in this case), the amount of radium energy will be $\frac{1}{4}$ x $\frac{1}{4}$ = $\frac{1}{16}$ of the original amount, or 100 mg. hrs. Likewise, at 3 cm. distance it will be $\frac{1}{9}$ the original; and at 5 cm. distance it will have reduced in strength to $\frac{1}{25}$ of the original strength at the point of irradiation. The same law of physics is equally applicable to roentgen rays. For practical purposes it should now be evident why it is impossible with radium alone to get enough irradiation into the pelvic lymph nodes (stage III and IV cases) without overirradiation of the structures adjacent to the cervix, such as the bladder and rectum. It is likewise easy to see that it is impossible to get enough irradiation safely into the parametrium and pelvic lymph nodes by roentgenotherapy alone to entirely eradicate cancer cells there without doing too much damage to the skin and other structures by the penetration of the roentgen rays. One should understand from a knowledge of this inverse square law why it is possible to always give enough radium safely to destroy practically all early (stages I and II) cancers of the cervix. The author should like to mention this fact because it is for these early cases that general surgeons and even many gynecologists still believe in surgical removal by panhysterectomy.

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* A colpostat is a special type of radium applicator, which is made in such a way that two radium containers, rubber or cork, are on either end of a 6 cm. steel spring. When inserted into the vagina, the spring straightens, thus carrying the radium as far toward the parametrium as the vagina permits.

Many steps have been taken to counteract this loss of irradiation energy resulting from the inverse square law: (1) Roentgenotherapy increases the amount of irradiation in the parametrium and pelvic lymph nodes. The roentgenotherapy tube is always directed toward the parametrium and never toward the cervix. As mentioned before, the radium will at all times take care of the malignancy of the cervix. (2) Colpostat technics, i.e., the Regaud or Kaplan colpostats, have been used very much in some clinics. A colpostat has two functions, to prevent overirradiation of the bladder and rectum, and to carry the source of irradiation as far laterally toward the parametria as the vaginal wall will allow from the spring action of the colpostat. (3) All forms of interstitial, either intra-abdominal or pervaginal, radium therapy are used for the same two purposes: (*a*) to get the point source of irradiation directly in the area of extension, i.e., parametria and pelvic lymph nodes, and (*b*) to prevent overirradiation of the bladder and rectum. Parametrial interstitial implantation has several advantages so far as the ultimate cure of cancer is concerned, but it also has two serious disadvantages. These are: the infection that occurs in a few cases, and the damage to the ureters with subsequent fibrosis, stricture and pyonephrosis. Recent literature shows fewer such complications than formerly from interstitial implantation of radium.

COMPLICATIONS FROM IRRADIATION

It is hardly justifiable to write a paper on radiotherapy without discussing the complications. The most common complications for cancer of the cervix are the following: (1) The usual irradiation sickness is very common, practically never serious, and generally presents no problem. (2) Infection, even an occasional pelvic cellulitis, may occur. Roentgenotherapy used before radium usually lessens the incidence of infection from radium treatments. Parametrial interstitial implantation of radium has the highest incidence of infections of any type of irradiation for cancer of the cervix. (3) Cystitis or proctitis may occur. There is practically always a certain amount of irradiation reaction with urinary frequency and a tendency to diarrhea, but this usually clears up within two to four weeks without aftereffects. An occasional case is left with permanent injury. Vernon David (18) reported six such cases. Dean (19) estimated that 2.1 per cent of all cervix cancers treated by irradiation have bladder injury with late atrophic changes, ulceration, and similar conditions. These are always painful and hard to control. (4) Rectovaginal and vesicovaginal fistulas occur in 5 to 10 per cent of all cancer of the cervix cases treated by irradiation. Smith (20) estimates that these fistulas will develop spontaneously from extension of the disease twice as frequently as those treated by irradiation. Pitts and Waterman (21) recently reported an incidence of 7.9 per cent fistulas in cancer of the cervix treated by interstitial radium and roentgen therapy. The four reasons for fistula formations are overirradiation, spontaneous extension of the growth destroying the rectovaginal or vesicovaginal septum, destruction of the cancer of either septum by irradiation, and direct contact with radium from improper application. Fistula formations are most often seen following irradiation of cervical stump cancer. (5) Irradiation injuries to the skin of the pelvis from overirradiation are not common when carefully done by the present-day fractional dose technic. (6) Radium necrosis of the cervix occasionally occurs from overdosage or insufficient filters. There are other complications but they are usually not as common or serious as the ones mentioned. Irradiation complications are painful, hard to heal, and can usually be avoided.

Causes of death in cervix cancer. It is not always easy to find the direct cause of death in many cancers of the cervix. Autopsy records reveal that approximately 25 to 40 per cent of all cases have obstruction to the ureters with its sequelae, i.e., hydro-ureter, pyonephrosis, and occasionally uremia. Parametrial extension will be found in 35 to 50 per cent of all cases coming to autopsy. Morton (22) found disease still present in the cervix at operation in approximately 50 per cent of cervix cancer treated by irradiation. The author believes Morton's cases probably did not receive enough irradiation; however, his study does show that many of these cancers may have been radioresistant. Distant metastases will be found in 25 to 40 per cent of all cases at autopsy. The organs most commonly showing remote metastases are in order of frequency: liver (20 per cent), lungs (10 per cent), and bone (5 to 7 per cent). Distant metastases are more frequent in untreated cases.

RESULTS OF TREATMENT

Results of treatment by radiotherapy. The author noticed three facts in a fairly extensive review of the literature on the five-year survival rates of cancer of the cervix treated by irradiation therapy: (1) The similarity in the percentage of five-year cures from nearly all the large cancer clinics of the world. (2) The increase of the five-year cures in the present literature as contrasted to that of previous years from the same clinics. (3) The clinics using the continous dose (Regaud) technic or the divided dose (Heyman) technic usually had a slightly better percentage of five-year cures than the clinics using the massive single dose technic of radium therapy. A résumé of the recent literature on five-year cures of cancer of the cervix treated by radiotherapy from nearly all the large clinics of the world is about as follows:

Stage I—60 to 80 per cent of cancers of the cervix have five-year cures
Stage II—40 to 60 per cent of cancers of the cervix have five-year cures
Stage III—20 to 30 per cent of cancers of the cervix have five-year cures
Stage IV— 0 to 10 per cent of cancers of the cervix have five-year cures

Results by surgery. Surgical removal should no longer be the procedure of choice in the treatment of cancer of the cervix. The future may show that Taussig's (23) operation, parametrial and pelvic lymph node dissection following radium therapy to the cervix, is a justifiable procedure. He does that operation for the same reason that axillary dissections are done in cancer of the breast. Victor Bonney (24) and Wertheim (25) are the great advocates of surgical removal of cervix cancer by panhysterectomy with extensive pelvic dissections. Their five-year cures, which sum up fairly well the present status of surgery, are as follows: Operable cases 40.6 per cent (Bonney) and 41.3 per cent (Wertheim); all type cases, operable and inoperable, 24.4 per cent (Bonney) and 19 per cent (Wertheim).

SUMMARY AND CONCLUSIONS

1. The incidence, gross and microscopic pathology, etiology, symptoms, and clinical stages of cancer of the cervix were reviewed briefly.
2. The present status of the various methods of roentgenotherapy were given. Supervoltage and pervaginal roentgenotherapy are too new to be of established value. Roentgenotherapy has been a definite factor in the increased percentage of five-year cures, especially the stage III cases.
3. The various technics of radium therapy were discussed in detail. The continuous or divided dose technics gave better results than the massive single dose technics.
4. The importance of the inverse square law in the physics of irradiation and its practical significance were shown.
5. Complications of radiotherapy may occur and were discussed briefly, but they are usually not common with present-day radiotherapy.
6. The common causes of death in cervix cancer were reviewed. Two facts were observed, the high incidence of obstruction to the ureters and the low incidence of general metastases.
7. Results of treatment by irradiation and surgical removal were given. There has been no increase in five-year cures by surgery, but

there has been a constant improvement in results by radiotherapy. Heyman (26) reported on 3512 cases treated by irradiation in 1927 from seventeen of the largest clinics in the world. The percentage of five-year cures was 16.3. Swanberg (27) recently reviewed 1431 cases of five-year cures treated by irradiation in 1932 from sixteen large clinics. The results were as follows:

Stage I—67.7 per cent cures
Stage II—44.1 per cent cures
Stage III—24.2 per cent cures
Stage IV— 6.5 per cent cures

The best results reported from any clinic in the world so far are those from the Radium Institute of the University of Paris, where 51.5 per cent of all cases (stages I to IV) had five-year cures.

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CLINICAL EXPERIENCES WITH STILBESTROL, A SYNTHETIC ESTROGEN*†

(Preliminary Report)

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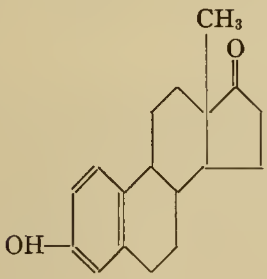
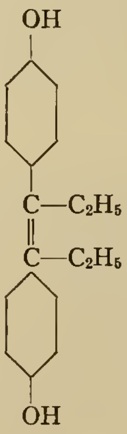
INTRODUCTION

In 1938 Dodds and his coworkers (1) in England announced the synthesis of a new estrogen, diethylstilbestrol (4–4′ dihydoxy a. b. diethyl stilbene). This substance, which can be synthesized in an economical yield from ordinary chemical starting material, was found to possess an estrogenic activity greater than that of estrone (2). It was formerly thought that the phenanthrene nucleus was necessary for a substance to possess estrogenic activity. However, Friedmann (4) in 1935, and Dodds and Lawson (5) in 1936 showed that the phenanthrene ring is not necessary for estrogenic activity. Dodds (3) reports, "that the body does not demand absolute specificity, certain for its estrogenic reactions, and if it is possible to obtain substances with a high degree of activity which bear little or no relationship to the estrone molecule, it is a fair deduction to make that other hormone processes may yield to the application of a similar type of investigation."

Estrone (Phenanthrene Nucleus)



Stilbestrol



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* From the Department of Gynecology, Sinai Hospital, Baltimore, Md.

† Received for publication March 28, 1940.

ACTIVITY

Dodds (2) found that stilbestrol possesses an activity greater than estrone. It proved to be two and one-half times as potent as estrone in the production of cornified smears (1). In addition, this new compound exhibited the properties of the natural estrogens in the production of uterine growth, mating in the castrate animal, nipple growth, and hen feathering, and abolished the castration cells in the anterior lobe of the pituitary (6). This synthetic estrogen also inhibited lactation in rats, altered the composition of cow's milk, and inhibited the response of the crop gland of pigeons to injections of prolactin (7). Administration of stilbestrol by mouth prevented the implantation of embryos or interrupted pregnancy after implantation had occurred in rats (8).

In the report to the Therapeutic Trials Committee, Bishop et al. (9) conclude that the oral administration when withdrawn produced "estrin withdrawal bleeding; produced an estrogenic type of endometrium both in the human female and in the monkey; induced growth of the hypoplastic uterus; relieved symptoms of the menopausal syndrome; converted a menopausal into an estrus type of vaginal smear; restored the normal appearance of the vulva and vagina when they have become atrophic as the result of the estrogen deficiency of the climacteric; induced painful swelling of the breasts; caused proliferation and activation of the epithelium of the mammary glands; relief of pain in dysmenorrhea."

Kreitmair and Sieckmann (10) found stilbestrol to be twenty times more active than estrone and five or six times more active than estradiol benzoate given by mouth in rats.

According to a number of workers (11, 12), a milligram of stilbestrol is equivalent to 25,000 international units of estrogen.

TOXICITY

Some investigators have reported disagreeable untoward reactions, the principal ones being gastro-intestinal disturbances. As a result, use of the drug is criticized. Shorr and his colleagues (13) report toxic manifestations other than those noted by most observers. These are in addition to alimentary tract reactions (nausea, vomiting, abdominal distress, anorexia, and diarrhea), lassitude, paresthesia, vertigo, thirst, an acute psychotic reaction, and cutaneous rashes. Many authors report few toxic symptoms, whereas others believe they are of sufficient intensity to interdict the use of the drug. In this report of the experiences with the medication in sixty-six cases, twelve reported nausea and three vomiting. No other disagreeable effects were noted. And in these, with changes in dosage and the use of antacids, tolerance was established. These findings coincide with many of the other investigators, particularly the English (2, 9, 11, 14, 15).

In animal experimentation there is not yet complete agreement. Kreitmair and Sieckmann (10) found that a dose of 300 mg. administered subcutaneously to a small dog produced no secondary symptoms. On the other hand, Loeser (17) noted injurious effects on the adrenal glands and livers of rats after large doses. Morrell (16) has failed to observe any pathological changes in the tissues of rats, rabbits and monkeys.

There may be differences in the chemical purity of the products used by the various workers to account for the divergence of results. The English have constantly shown slight toxic effects. Dodds (18) in his early work found that contaminants were responsible for high estrogenic activity (polymers). It is possible that further purification may eliminate these unpleasant reactions.

CLINICAL RESULTS

In April, 1938 stilbestrol* was introduced in the clinic of Sinai Hospital which was primarily interested in the climacteric. For a period of eleven months the effects of this drug were studied in sixty-six white patients ranging in age from twenty-one to sixty years. Results have been satisfactory and it is believed that the synthetic estrogen, stilbestrol, will prove a valuable adjunct to the armamentarium in the treatment of endocrine disturbances. At first parenteral dosage was utilized but it was soon found that the oral administration was just as effective and less bothersome. The necessity of using hypodermic injections and the cost of medication and administration are objectionable features in present-day endocrine therapy. It was necessary to re-educate many of the patients who came expecting "needle treatments." One of the most gratifying results was the rapidity with which symptoms disappeared by merely taking a few doses orally and in a number of cases after a single 5 mg. pill.

There were forty-two cases of the physiologic climacteric. Eighteen women responded quickly and effectively, with relief of symptoms. Twelve required longer treatment and did not obtain complete relief of their complaints. In this group there were four who were not helped at all. Two of the latter were reluctant to continue treatment because of the nausea.

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* Stilbestrol obtained from E. R. Squibb & Sons through the kindness of Dr. J. A. Morrell.

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Artificial climacteric in eight women responded satisfactorily to therapy, five with good results and three fair. (These terms are qualitative; however, their meaning should be clear.)

Two young women with primary dysmenorrhea were not relieved and medication was discontinued. One patient with galactorrhea was effectively treated.

Six patients with amenorrhea showed satisfactory results. Restoration of the menstrual cycle was effected in five with secondary amenorrhea, and a good psychic result was produced in one patient with a withdrawal type of bleeding. One mg. of the drug was given daily for two weeks corresponding to the proliferative phase.

CASE REPORTS

Several typical cases are presented briefly.

No. 1. A patient 51 years old had been in menopause for four years. She had seven or eight hot flushes per day, followed by profuse sweats. Nervousness and indigestion were persistent. Stilbestrol in doses of 5 mg. was given daily by mouth. After two weeks of treatment there were no hot flushes and in general the patient was considerably improved. A vaginal smear changed from a menopausal type to one typical of estrogenic response (19). Therapy was continued. Six weeks after the onset of treatment with 5 mg. daily a slight vaginal bleeding was noted. The dosage was then diminished to 1 mg. daily. All symptoms were relieved.

No. 16. This patient was 48 years old. Her menstrual periods were irregular, and she had hot flushes nine to ten times daily. These were followed by chills and associated with headaches and nervousness. Her libido was normal. She was given 5 mg. of stilbestrol orally every other day. After one dose the symptoms disappeared. When the medication was discontinued there was a return of her complaints. The patient was then given a maintenance dose of 1 mg. per day with complete relief. No vaginal smears were obtained.

No. 36. In this patient of 29 years artificial menopause followed an operation three months before consultation. She had hot flushes every fifteen minutes, with a desire to tear all clothing from her body. Chills and sweats followed, also extreme nervousness and severe headaches. Stilbestrol was prescribed in doses of 0.1 mg. three times a day by mouth. The patient returned in one month and asked for more stilbestrol because this treatment had proved so effective. She was placed on 5 mg. daily with complete relief of symptoms.

No. 9. This patient was 38 years old and extremely nervous. She had hot flushes every half hour, followed by chills and headaches. Her periods were regular and she was hypertensive. Stilbestrol was prescribed in doses of 5 mg. daily by mouth. After 70 mg. no relief or toxicity was experienced. The patient was then placed on natural estrogens and sedatives; she received no relief and at present is still under treatment.

DOSAGE

Treatment should be individualized according to the severity of symptoms. Accordingly, if mild, one may begin with small doses, 0.1 mg., daily or several times a day, or one may give 5 mg. every other day. As the patient improves, the amount of drug given is diminished. If the symptoms are severe, 5 mg. daily and two intramuscular injections weekly may be administered. The parenteral route is used infrequently. Enough of the estrogen is given the patient to last one week, at the end of which period it may be determined whether toxicity to the drug exists and the efficacy of treatment. Adjustments can then be made and sufficient medication given to last two or three weeks. Bicarbonate of soda and milk of magnesia are used to combat nausea and vomiting. In every case where the patient was willing to cooperate, this unpleasant reaction was eliminated by adjusting the dosage and the use of antacids.

DISCUSSION

The unpleasant symptoms accompanying the climacteric can be effectively relieved by stilbestrol, the synthetic estrogen. This drug should be much cheaper than the natural estrogens. That it is efficacious by mouth is a great advantage and eliminates the troublesome parenteral method. Every patient should be completely studied, including the basal metabolic rate, and therapy individualized. It is true that this study includes only sixty-six cases, but the results have been satisfactory, with little toxicity. A number of patients received over 100 mg. per month with no reaction. The nausea and vomiting can be controlled.

SUMMARY AND CONCLUSIONS

1. The activity of a synthetic estrogen, stilbestrol, is described.
2. The toxicity of the drug is discussed and a variance of conclusions shown. The disagreeable untoward reactions were slight and easily amenable to correction.
3. Stilbestrol was used in sixty-six cases, and the results in fifty-one cases reported. The remainder of the cases were not complete enough to report, except for tolerance. These will be described in a later paper. Case studies are given in a number of typical examples.
4. A plan of therapy is outlined, the dosage depending upon the severity of symptoms. The parenteral route is used infrequently. Nausea and vomiting can be controlled with small dosages of sodium bicarbonate and milk of magnesia. The maximum dosage given was 45 mg. weekly.

The author wishes to gratefully acknowledge the kindly advice of Dr. Alfred Ullman, Chief of the Surgical Division of Sinai Hospital.

Sincere appreciation is due Dr. Abram S. Samuels and Dr. A. Adler Sondheimer of the Department of Gynecology, Sinai Hospital, for their guidance and assistance.

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A SURGICAL TREATMENT OF GRANULOMA INGUINALE*†

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Many and varied types of treatment have been tried in granuloma inguinale, none of which has been uniformly successful. Tartar emetic administered intravenously and fuadin intramuscularly are considered the most successful drugs in use. Roentgen ray, sunlight, fulguration, and daily baths have all been used. Even when healing is complete there is frequently marked deformity caused by tissue destruction and scar formation (1). No matter how successful the drug is in eradicating the disease it will not cure pre-existing deformity.

The following is a case report in which the patient received no previous treatment and developed considerable deformity.

CASE REPORT

R. W., No. 31430, a colored male, age 30 years, was first seen in the dermatology clinic of the University Hospital dispensary in the first part of March, 1940 and referred to the Department of Urology for a plastic operation. At that time he gave a history of having had the disease for about one year. The first symptom was a "lump" on the glans penis (probably a papule). This later broke down into an ulcer and gradually extended around the corona. The scrotum gradually became enlarged owing to lymphedema. Approximately eight months previous to his coming to the clinic the penis disappeared into the skin covering the scrotum and the pubic area overnight, according to the patient. In all this time he had received no treatment, but had kept the parts clean with soap and water. When first seen the scrotum was about the size of a grapefruit (Fig. 1). On the anterior surface there was an ulcerated area about 8 by 5 cm., the center of which was a nonpigmented scar approximately 3 cm. in diameter. The urine was passed through a small fistula near the center of this area. The periphery was the typical piled-up ulcer of a granuloma. The shaft of the penis and the testicles could be palpated in the scrotum in their normal relation to each other.

The patient was admitted to the hospital and given the routine examinations and study; nothing of unusual bearing on the case was found. However, a curious situation presented itself. It was imperative that some type of plastic repair be done as the urinary stream was diminishing. This in time would produce obstruction, cystitis, pyelitis, and eventually kidney damage. Also, these cases frequently develop a psychological disturbance of some form. The operation must allow for urinary drainage as well as repair of the defects. Several types of operation were studied.

A complete emasculation could be done. This would have been the simplest operation but was discarded as being too radical. Next, the idea of dissecting the penis from the scrotum and covering it with a skin flap taken from part of the

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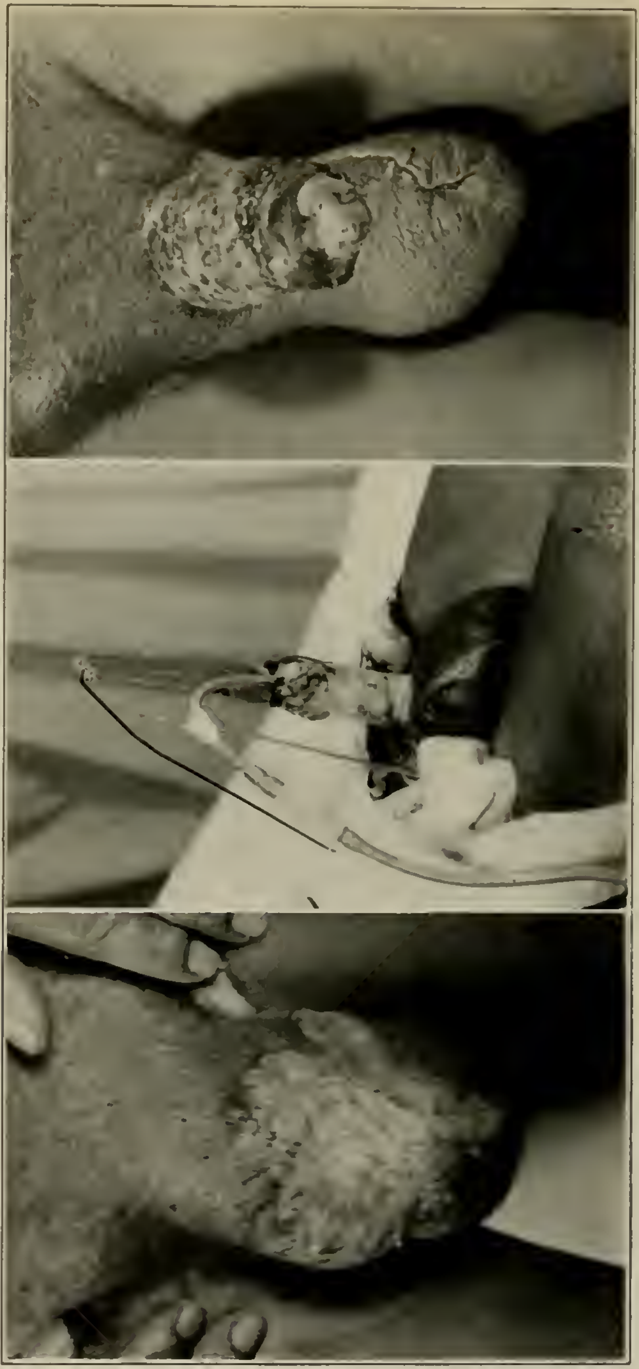

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Scrotum before operation showing ulcerated area with scar formation in the center.
Fig. 2. Apparatus for holding penis under tension and facilitating urinary drainage.
Fig. 3. The final results showing pinch grafts and line of closure on the scrotum.

scrotum or skin from the abdomen was considered, but this would have necessitated suprapubic or perineal drainage of the bladder. In this case there would probably have been difficulty in obtaining sufficient skin, and part of the area was secondarily infected. Therefore, the following two-stage operative procedure was finally adopted.

Under spinal anesthesia the first operation was done. The ulcerated area was excised, the incision being made about 1 cm. beyond the diseased area, down to the subcutaneous tissue. After the skin incision was made the electric cautery knife was used to dissect the shaft of the penis free from the surrounding tissue. This excess tissue was found to be fibrous and poorly supplied with blood vessels. It was dissected from the periphery to the attachment of the penis to the scar tissue area. This was the last part severed from the penis, and two silver wire sutures were placed through what was thought to be the glans penis. It was quite fibrous and practically bloodless. A No. 20 soft rubber catheter was passed through the urethra and held in place by tying a piece of catgut about the catheter and passing the ends through the glans. In the future a Foley self-retaining catheter will be used. The skin of the scrotum was sutured with dermol and the testicles maintained in normal position. A gutta-percha drain was inserted under the skin and a dry gauze dressing placed about the shaft of the penis. The wire sutures were attached to a wire framework by means of rubber bands which held the denuded penis upright and under some tension. Urinary drainage was through the catheter (Fig. 2). After the second day the dressing was kept wet with a saturated solution (12½ per cent) of sodium sulfate (2).

The postoperative course was fairly smooth. The temperature of the patient was elevated for five days and reached a maximum of 103° F on the second day. After three weeks of sodium sulfate treatment the denuded penis developed a clean granulating surface and was ready for skin grafts. The scrotum had in the meantime healed. Under spinal anesthesia the penis was covered with half thickness pinch grafts taken from the thigh. At the time of the second operation the wires had sloughed through and it was found that what was previously thought to be the glans was in reality the foreskin, and an intact glans penis was found underneath. After a vertical duckbill incision had been made wire sutures were placed through these two wings formed by the foreskin. A catheter was inserted for drainage and the penis again put under tension by means of the same apparatus that was used previously.

The grafts were kept in place by a collar of poro-wax gauze, and the dressing was moistened with normal salt solution. After ten days the grafts had taken, all dressings were removed, and the entire area exposed to atmospheric air to dry and toughen the grafts. The tension apparatus was left in place for five more days and then removed. Several days later, under pentothol sodium anesthesia the remains of the foreskin were removed with the electric cautery and the raw area cauterized. Eight weeks after the first operation the penis was healed and covered with skin, except for a small area about the corona where the foreskin was removed (Fig. 3). The patient is receiving antimonium tartrate treatment from Dr. H. M. Robinson, Jr., who demonstrated Donovan bodies in the different pieces of tissue removed (3).

CONCLUSIONS

This unusual surgical procedure is presented as a type of treatment to be used along with a form of antimony therapy. It is felt that the use of sodium sulfate solution greatly aided the formation of granulation tissue and facilitated healing.

Another case of this type has had the first stage operation performed and is progressing. Several others are awaiting operation. If these have as satisfactory results as the first, a method will be presented that will shorten the disability period and prevent a great deal of psychic-producing deformities.

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SULFAPYRIDINE IN GONORRHEA*†

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This series consists of forty male patients who were selected because they were recently infected and had received no previous treatment. However, in four cases an adequate course of sulfanilamide had been given and proved unsuccessful. In this series of forty cases, thirty-two were treated with sulfapyridine alone and were not given any form of local treatment. The other eight were given local treatment arbitrarily.

Some internists have been using sulfapyridine in pneumonia in doses of 180 grains per diem. All cases of adults in this series were started with 90 grains administered in doses of 15 grains every four hours, day and night. In most cases of the 90-grain group, the drug had to be discontinued after forty-eight hours and in some it was necessary to decrease the dose after twenty-four hours on account of toxic symptoms, as all of these patients were ambulatory. In some of the cases sodium bicarbonate was given but no effect was evident in diminishing the toxicity of the sulfapyridine in this combination.

Wien (1) determined while experimenting with mice and rats that sulfapyridine was only about one-quarter as toxic as sulfanilamide.

Toxic effects were not manifest in this series until about 60 to 75 grains of the drug had been taken. The following effects were noted: Most patients having had that amount, i.e., 60 to 75 grains, complained of headache and some of dizziness. However, this dizziness was not of a severe character. It was difficult to determine cyanosis since 77½ per cent of these patients were colored. This symptom was noted in 33⅓ per cent of the white patients. Thirty per cent of all cases had vomiting, which was not severe as they vomited but once or twice. Practically all patients, after receiving 60 grains, complained of nausea. The drug was not withdrawn on complaint of nausea but was withheld from all cases as soon as vomiting appeared. All patients were instructed to discontinue it on severe nausea or vomiting. It might be added here that negroes tolerated larger doses than white patients. Blonds seemed to be more intolerant to it than the heavier pigmented types. Therefore, caution as to dosage is suggested in blonds and so-called titians. The toxic effects of the drug disappeared in twenty-four hours after its withdrawal in all but one case, and in this man nausea and headache persisted for three days after its discontinuance.

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† Read before the Mid-Atlantic Branch of the American Urological Association, Washington, D. C., on April 6, 1940.

In 12½ per cent of the cases the age of the patient was under twelve years, the youngest being five years of age. The dosage in this group was graduated accordingly, the smallest dose being 0.25 gram every four hours for forty-eight hours.

It has been reported by Tsao (2) of China and also by Shea (3) of St. Louis that in cases of pneumonia in which large doses of sulfapyridine were used there was marked incidence of hematuria. The obstruction of the ureters by acetylsulfapyridine crystals proved fatal in one of Tsao's cases. Since hematuria may be a prodromal sign of the formation of acetylsulfapyridine calculi in the urologic tract, these cases were watched carefully for this symptom. No hematuria was noticed in this series. In those cases where the drug was stopped, the patients were instructed to drink 6000 cc. of water in twenty-four hours for several days so as to prevent the accumulation or the persistence of acetylsulfapyridine crystals in the kidneys, ureters and bladder, and thus curtail the possible formation of urinary calculi. While the patients were on active medication the fluid intake was restricted to a minimum to allow greater concentration.

A blood level of sulfapyridine was determined in 37½ per cent of the cases after forty-eight hours of active medication, i.e., in cases receiving 180 grains in that period. These tests showed concentrations ranging from 2.45 to 15 per cent. The concentration did not seem to be in relation to the clinical response, as one of the forty-eight hour negative smears was obtained in the case that had the lowest blood level of any, 2.45 per cent.

In 10 per cent of this series the men had previously had sulfanilamide and this drug had failed to produce negative smears. All of these men showed negative smears after being treated for the following number of days with sulfapyridine: three had negative smears in two days, one of whom had a negative culture on the twenty-third day; one had a negative smear in four days, with a negative culture thirty-nine days later.

Thirty-two of these cases were not given any form of local treatment and, as stated previously, eight were given local treatment arbitrarily. The smears became negative in these thirty-two cases as follows:

16 hours	1 case	3 days	7 cases
1 day	4 cases	4 days	3 cases
2 days	10 cases	5 days	3 cases

There were four, or 12½ per cent, failures. Cases that showed positive smears more than ten days after the institution of treatment were considered failures. Of these, one had positive smears for eleven days, one for twelve days, one for thirteen days, and one for fifteen days. At the expiration of these respective days other treatment was started.

No complications developed in this series of cases, although 15 per cent had epididymitis and 5 per cent had acute prostatitis when applying for treatment. Very marked improvement was noticed in the cases of epididymitis.

CONCLUSIONS

1. The drug should be continued over a more lengthy period but after forty-eight hours it should be decreased in dosage. For example, 30 to 40 grains a day for two or three days should be used after the termination of the large initial dose of 90 grains for twenty-four hours in the first two days of treatment. The dosage should then be decreased gradually until the patient has had the treatment for ten days.
2. If local treatment can be used with the sulfapyridine, as in uncomplicated cases, it will hasten recovery.
3. Sulfapyridine treatment has very marked value in children suffering with Neisseria infections, so many of whom are seen in the colored race in large cities.
4. Although sulfapyridine failed in 12½ per cent of the cases in this series it seemed to diminish the virulence of the infection, as none of the failures developed further complications and a marked clinical improvement was noticed in epididymitis.
5. Culture controls should be obtained in all cases and again repeated in three to six months after the cessation of treatment.

Grateful acknowledgement is hereby given to Dr. W. G. Malcolm of the Lederle Laboratories for the supply of the drug which made this study possible.

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PNEUMOCOCCUS MENINGITIS IN INFANTS*†

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Pneumococcus meningitis, once so universally fatal, is now on the ever-increasing list of diseases in which chemotherapy is reducing mortality and morbidity. Hodes, Gimbel and Burnett (1) have recently reported eight cases of recovery out of seventeen treated with sulfapyridine. Other cases of recovery by means of the same treatment have been reported (2, 3, 4, 5, 6, 7, 8, 9, 10).

To date, however, the results in infants, even with sulfapyridine, have been poor. All of the four children under twelve months of age in the Hodes, Gimbel and Burnett series died. Aitchison (11) also reported a case in a child twenty months old with a fatal outcome, in spite of the use of sulfapyridine.

It is the purpose of this paper to report a case of pneumococcus meningitis type III in a child nine months of age, in which sulfapyridine was used with complete recovery. This, as far as the author can determine, is the youngest infant reported to have recovered with the use of sulfapyridine. The importance of early diagnosis of this condition in infants should be stressed so that treatment may be begun promptly.

CASE REPORT

A. B., nine months old, was admitted to the pediatric service of the Sinai Hospital on January 13, 1940. He had frequent colds throughout the fall and winter. Ten days prior to admission, he had bilateral otitis media and an upper respiratory infection, from which he was apparently improving on January 11, 1940. At 2 a.m. on the morning of admission (January 13) the patient awakened screaming. This recurred several times until 6 a.m. At 7.30 a.m. he vomited and again fell soundly asleep. He slept until 2 p.m., when he was seen by the author. At that time he had a temperature of 103°F., with a respiratory rate of 40. He was extremely toxic, drowsy, and irritable. The patient was pale, his tongue was thickly coated, and the pharynx was covered with thick mucus. An examination of the ears showed a mild infection. The eyes were negative, and the lungs were clear to percussion and auscultation. His deep and superficial reflexes were normal. There was no bulging of the fontanel, no Kernig's sign, no stiff neck, and no strabismus. Examination of the blood showed: hemoglobin 56%; red blood cells 3,610,000; white blood cells 19,250; polymorphonuclears 72%; lymphocytes 28%. Examinations of the urine and stool were negative. The tuberculin (0.1 mg.) and Wassermann tests were negative.

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* From the Pediatric Service of Sinai Hospital, Baltimore, Md.

† Received for publication March 11, 1940.

TABLE I

Summary of Laboratory Data

	JAN. 16	JAN. 17	JAN. 18	JAN. 19	JAN. 20	JAN. 21	JAN. 22	JAN. 23 TO JAN. 28	JAN. 28	FEB. 2
Sulfapyridine Dosage	1⅓ gms., 5:30 P.M. ⅓ gm. q.4.h.	2 gms. at 4 P.M. Total 4⅓ gms.	6½ gms.	7 gms.	3⅓ gms.	4½ gms.	5 gms.	6 gms.	6 gms.	6 gms.
Sulfapyridine Concentration in Blood		10 mg. %	3.2 mg. %	20 mg. %	7 mg. %	4.6 mg. %		4.5 mg. %	6.2 mg. %	
Sulfapyridine Concentration in C.S.F.		2.7 mg. %								
WBC. in C.S.F.	11,000/cm. 90% PMN. 10% L.								7/cm. 2 PMN. 5 L.	
C.S.F. Culture	Type III Pneum.	Neg.							Neg.	
Blood Culture	Negative									
Ear Culture	Negative									
WBC. (Blood)	24,000 78% PMN. 22% L.		20,000 70% PMN. 28% L. 2% M.	16,000	12,000 72% PMN. 24% L. 4% M.	9,400 70% PMN. 30% L.	9,600 72% PMN. 24% L. 4% M.	9,200 73% PMN. 24% L. 3% M.	11,440 66% PMN. 31% L. 3% M.	10,800 66% PMN. 32% L. 2% M.
Hg.	82%		80%	80%	80%	80%	82%	80%	80%	80%

Course in the hospital. The temperature remained elevated, between 103 and 104°F. An examination on January 14 revealed slight impairment of the left lung which was interpreted from a roentgenogram as a small pneumonic area. Both ears were incised and cultures from them were negative. On the following day the patient remained drowsy and irritable, and a transfusion of 150 cc. of citrated blood was given with immediate mild convulsive movements of both arms and yawning which lasted 15 minutes. On January 16 a spinal puncture was done and opalescent fluid released under normal pressure. The cell count on the spinal fluid was 11,000 white blood cells per cm., 90% of which were polymorphonuclears. Mouse typing of this fluid showed type III pneumococcus. One and one-half gm. of sulfapyridine were given orally at 5:30 p.m. At 6 p.m. the temperature dropped to 101.6°F. It was normal the next morning and remained normal for the rest of the course in the hospital. Sulfapyridine was continued at the rate of 6 gm. per day, and the level in the blood was kept at an average of about 10 mg.%, the highest level being 20 mg.%.

On January 17 the child appeared much better and had apparently no ill effects from the sulfapyridine. Spinal puncture on the same day showed the culture to be sterile and the sulfapyridine level 2.7 mg.%. The remainder of his course in the hospital was entirely uneventful and on January 28 examination of the spinal fluid was negative. There were 7 white blood cells per cm. and the culture was negative. The Pandy test also proved negative. Two days later sulfapyridine was discontinued and on February 8 the patient was discharged as cured.

COMMENT

Pneumococcus meningitis occurs more frequently in infants than in older children, according to Holt (12). He found that over half the cases seen in children were in patients under six months of age. More recently Cable (13) reported a series of thirty-nine fatal cases in which twenty-four were under ten years of age and nine cases under one year of age. In the past ten years there have been twelve cases of pneumococcus meningitis on the pediatric service of the Sinai Hospital. Of these, eight were infants under twelve months of age.

The diagnosis of pneumococcus meningitis in infants may easily be overlooked. The cardinal signs of meningitis are often absent. There may be no stiff neck, no Kernig's sign, no disturbances of reflexes, and no bulging of the fontanel. Often drowsiness and irritability are the only signs present. Spinal puncture should be done in all cases in which toxicity and drowsiness are present and where other examination fails to reveal evidence to account for these conditions.

SUMMARY

1. According to Holt, pneumococcus meningitis occurs more frequently in infants than in older children.
2. To date this disease is still extremely fatal to infants.
3. An early diagnosis is important so that sulfapyridine therapy may be begun promptly with the hope of lessening the mortality.

4. The author has presented what he believes to be the youngest infant with penumococcus meningitis to recover by treatment with sulfapyridine.

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DR. JOHN CRAWFORD, 1746-1813*†

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For many years the card catalog of the Medical Library of the University of Maryland has listed approximately four hundred volumes known as the Crawford Collection, but little has been written about Dr. John Crawford who assembled these volumes. An entry in Smith (29) gives the following information about him, but even this contains obvious errors:

> Crawford, Joannes. Hibernus, Sept. 22, 1794, aet. 48. Medicinae Doctor. M.D. St. Andrews, 1791. At Trinity College, Dublin, 1756, aet. 17. B.A. Dublin, 1760. Born North of Ireland in 1746. Brother of Adair Crawford, M.D. John Crawford entered East India Company's service. He later became Physician in Demerara. Made contributions to the Medical Commentaries in 1793. In 1796 went to Baltimore and died there, 1817. An early exponent of vaccination in America. Vide Kelly.

Dr. Eugene F. Cordell, the recognized authority on University of Maryland medical historical data, failed to mention some of the most interesting facts pertaining to Dr. John Crawford. The very manner in which the Crawford Collection came to the Medical Library is obscure, and some of the hitherto published accounts seem to be erroneous. The one established fact is that the Crawford Collection was the beginning of the Medical Library of the University of Maryland—one of the oldest libraries of its kind in this country.

Dr. John Crawford, a very prominent physician of Baltimore, was living with his daughter and son-in-law when he died in 1813. His daughter had married Maximilian Godefroy, a well-known French architect, who was to attain local recognition for his designs of the Battle Monument, the First Unitarian Church, St. Mary's Chapel on Paca Street, and many other outstanding structures in Baltimore. The family had been living in the vicinity of Hanover Street and German Lane, not far from the Indian Queen Tavern. (German Lane was then part of the street now known as Redwood.) The "Indian Queen" was the starting point of the daily stage to Philadelphia, a trip which in the early part of the nineteenth century took fifteen hours. Among the shops along Hanover Street was one belonging to Hugh and Jonathan Balderston, wire manufacturers, which stood opposite the

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* From the Library of the School of Medicine, University of Maryland.

† Received for publication May 20, 1940.

Indian Queen Tavern. These two men were witnesses to the will which Dr. Crawford made in 1810.

Although he had been practicing in the city since his arrival in 1796 (31),[1] Dr. Crawford was a man of modest means. He accumulated no fortune, but left a vast collection of books of which there was no equal then in the City of Baltimore. As a matter of fact, Crawford died greatly in debt. He tried to make provisions for the payment of his bills, especially the amount due George Kearsley, a London bookseller who had published one of Crawford's earliest works in 1772 "On a Disease of the Liver." The doctor must have ordered a quantity of expensive books from this London bookseller, judging from the very valuable collection which is now in the Medical Library of the University of Maryland. Crawford had hoped that through the sale of his library and the publication of his papers, the "just claims" against his estate could be settled. His obligations weighed heavily on his mind. He had even mentioned them to Dr. Benjamin Rush on one of his visits in Philadelphia. Dr. Rush recorded this meeting with his contemporary in his diary (8):[2]

> 1808
>
> Nov. 16
>
> This evening Dr. Crawford of Baltimore drank tea with me. He said his father was a clergyman in Ireland and that from 30 a year salary with the product of a glebe he had given four sons liberal educations and professions and left two daughters each 500 sterling.[3] The Doctor said he had lost all his business by propagating an unpopular opinion in medicine, namely, that all diseases were occasioned by animalculae. He said he was sixty-two years of age and not worth a cent, but in debt.

Crawford's will was filed and probated in the Baltimore County Court on June 19, 1813, but it was several months before it was executed. It is quoted here because of the light it throws upon Crawford's personal life. While to the casual observer Dr. Crawford's will might be lost among those of other luminaries of his period, nevertheless such a document has its place in source material for Maryland biography and history.

JOHN CRAWFORD'S LAST WILL AND TESTAMENT

In the name of God, Amen. I, John Crawford of the City of Baltimore, Physician, do make and declare this my last will and testament in manner following: I

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[1] Quinan (25) states that Crawford "arrived from Ireland" in 1776, but this is an error.

[2] Dr. Rush was born in 1745 and died in April, 1813; Dr. Crawford was born in 1746 and died in May, 1813.

[3] Dr. Adair Crawford, F.R.S., Edinburgh and London, one of Crawford's brothers, was quite famous in England through his scientific papers on "Animal Heat" published in *Medical Commentaries*.

give and bequeath to my son-in-law Maximilian Godefroy, my gold watch as a testimony of my affection and of the high degree of pleasure his conduct towards my Daughter and myself has given me ever since his becoming a member of my family. Also I give and bequeath to my valued friend Doctor William Donaldson, my Ivory headed cane, and all my manuscripts on medical subjects hoping and requesting that he will make such selections out of them as he may think fit for the public eye and have them published for the benefit of my estate, provided this can be done without subjecting it to any loss. Also I give and bequeath to my beloved friend Nicholas Le Favre, Esq. of Philadelphia, Gentleman, all my Masonic papers in full trust and confidence that he will employ some suitable Brother to select such parts of them as may in the opinion of James Milner, Esq. present Grand Master of Pennsylvania, and Samuel F. Bradford, Esq. present Grand Treasurer of the same state, be useful and safe to publish, and that the profits of these publications may be applied to the payment of my debts, particularly that which I owe to Mr. George Keasley, Bookseller in London. I will and direct that all the residue of my property estate and effects of every kind, including my Library of Books, shall be sold and the money arising therefrom applied to the payment of all just claims against me, and if any Balance shall remain, I give and bequeath same unto my Daughter Elizabeth Godefroy. Lastly, I do hereby constitute and appoint Nicholas Le Favre of Philadelphia, Gentleman, William Donaldson above mentioned Physician and William Gwynn Esq. Attorney-at-law, the two last of this city of Baltimore, Executors, and each of them executors of this my last will and Testament. In witness whereof I have hereunto set my hand and seal, and also to a duplicate hereof the first day of November in the year of Our Lord eighteen hundred and ten. Signed, sealed and published and declared by the Testator as his last will and testament, in our presence whom in his presence and at his request have hereunto
subscribed our names—Hugh Balderston JOHN CRAWFORD
Jonathan Balderston Seal
Samuel Peach

Within a month after Crawford's death in May, 1813, the executors of the will refused to serve, but in none of their depositions renouncing their trust is a reason for their action given. Nicholas Le Favre lived in Philadelphia and he probably found it impossible to make the trip to Baltimore at that particular time because of the imminence of fighting between British and local troops. Dr. William Donaldson and Mr. William Gwynn, an attorney at law, may have decided not to serve because of the personal indebtedness of the deceased.

It remained, therefore, for Maximilian Godefroy, his son-in-law, to seek letters of administration from the Orphan's Court. This he proceeded to do in the fall and the *Federal Gazette and Baltimore Daily Advertiser* first carried the announcement (13) on Tuesday, November 16, 1813.

Baltimore County Orphan's Court

3rd Nov. 1813
Present Owen Dorsey }
Corn's H. Gist } Esq.
Sam Owings of S. }
John Chalmers, Esq., Sheriff,—
Wm Buchanan, Reg.

Among others were the following proceedings, viz.: On application of Maximilian Godefroy, city of Baltimore, for letters of administration with a copy of the will annexed, on the personal estate of Dr. John Crawford, late of said county, deceased.

Ordered, that the Court will proceed to grant letters of administration, with a copy of the will, on said Maximilian Godefroy, on second Tuesday in December next, unless cause be shewn to the contrary, and provided a copy of this order be published in the *Federal Gazette*, in the city of Baltimore. twice a week for three weeks.

In testimony whereof I have hereunto set my hand, and affixed my seal of office this third day of November, Eighteen hundred and thirteen.

Wm Buchanan
Reg. Or. Ct. B. C.

These letters of administration were probably given to Mr. Godefroy, although no later records appear to verify this fact. Contrary to custom, there was no inventory. This was legal procedure since anything of value was sold in order to carry out the instructions of the will. The largest item was no doubt Crawford's library of books, consisting of at least four hundred volumes, which brought $500.00 (10). What remained in the estate had no significant value and no inventory was made.

It is interesting to note that Dr. Crawford left no widow, in spite of the following statements made by the basic authority, Dr. Eugene F. Cordell (Librarian of the University of Maryland Medical Library, 1903–1913): "The Faculty of the University of Maryland purchases Dr. Crawford's medical library from his widow (November)" (9). "The Library was founded in 1813 by the purchase of the books of the late Dr. John Crawford from his widow. This was accomplished by a subscription of $500.00 made for the purpose by the members of the Faculty" (10). The earliest manuscript records of the University of Maryland are dated 1826, when the Board of Trustees appointed by the Legislature took over the control of the University from the Board of Regents. If minutes or records were kept from 1807 to 1825 they have been lost or destroyed since Cordell wrote the above statements. Cordell gave no source for his assertions and it is, therefore, very difficult to trace all the facts related to the sentences just quoted.

Crawford's wife had died in 1782 and there is no evidence from any available records that he ever married again. On the contrary, he "never ceased to lament the remainder of his days" this very great loss in his life. The marriage bureau records of Baltimore list only two people by the name of John Crawford who were married in the period that Doctor Crawford lived in the city. St. Paul's Parish Registry, of which the Reverend Mr. Bend was the rector, records the marriage of a John Crawford and Jane Johnson on April 5, 1799. The other marriage cited is that of a John Crawford and Catherine Lucas on February 14, 1811 by the Reverend Mr. Roberts, for a short time minister of the First Methodist Church when it was located on Light Street and Wine Alley. There were many Crawfords in the city during this period, one of whom appears in the City Directory of 1799 as John Crawford (carter), resident on Bridge Street in Old Town (now East Baltimore). However, the subject of this study held a high position in the medical circles of Baltimore, and a record of a subsequent marriage would have identified him with his profession.

In addition to these facts, Dr. Crawford did not mention a wife in his will. All the original sources make references only to the daughter or to the son-in-law. There is a reference to the daughter in the *Proceedings of Cassia Lodge of the Masonic Order:*[4] "Feb. 13th, 1813.—The Treasurer was authorised to pay Mr. Bradford of Philadelphia thirty dollars for the engraving of the late R[ight] W[orshipful] G[rand] Master Dr. John Crawford, and the Brethren were requested to purchase copies of them at the rate of 50 cents; six copies were ordered to be presented to Mrs. Godefroy, the daughter of Grand Master Crawford" (28). (Fig. 1.) The only conclusion that can be reached in view of the paucity of details is that an error was made in relating that Crawford's widow sold his books. The Crawford Collection was purchased from the daughter, a woman of at least thirty-five years of age.

At the time of his death Dr. Crawford was the Right Worshipful Grand Master of the Masonic Order in Maryland. He had held this position from 1801 until his death, with but one exception. That was in May, 1806 when he declined the honor because of "private avocations." To further show their appreciation of Crawford's ability, the Masons had chosen him to be Grand High Priest of the Grand Royal Arch Chapter for the State of Maryland and the District of Columbia. His Masonic addresses delivered on various occasions are of a high moral tone, lofty in character, and worthy of the high state to which the Masons had elevated him. These papers were left to Nicholas Le Favre of Philadelphia, and whether any of them still exist has never been determined.

The Grand Lodge was holding its Annual Communication on May 3, 1813, when Crawford was re-elected Grand Master, and Dr. Tobias Watkins, Deputy. They adjourned the following night and were prepared to meet again the next morning, but news of an impending naval attack postponed the meeting.

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[4] Feb. 13, 1813 was either a typographical error or else Schultz (History of Freemasonry in Maryland) made a mistake in copying the proceedings of Cassia Lodge. All other entries are recorded as of 1814 and obviously that is the correct date, for Crawford did not die until May 9, 1813.

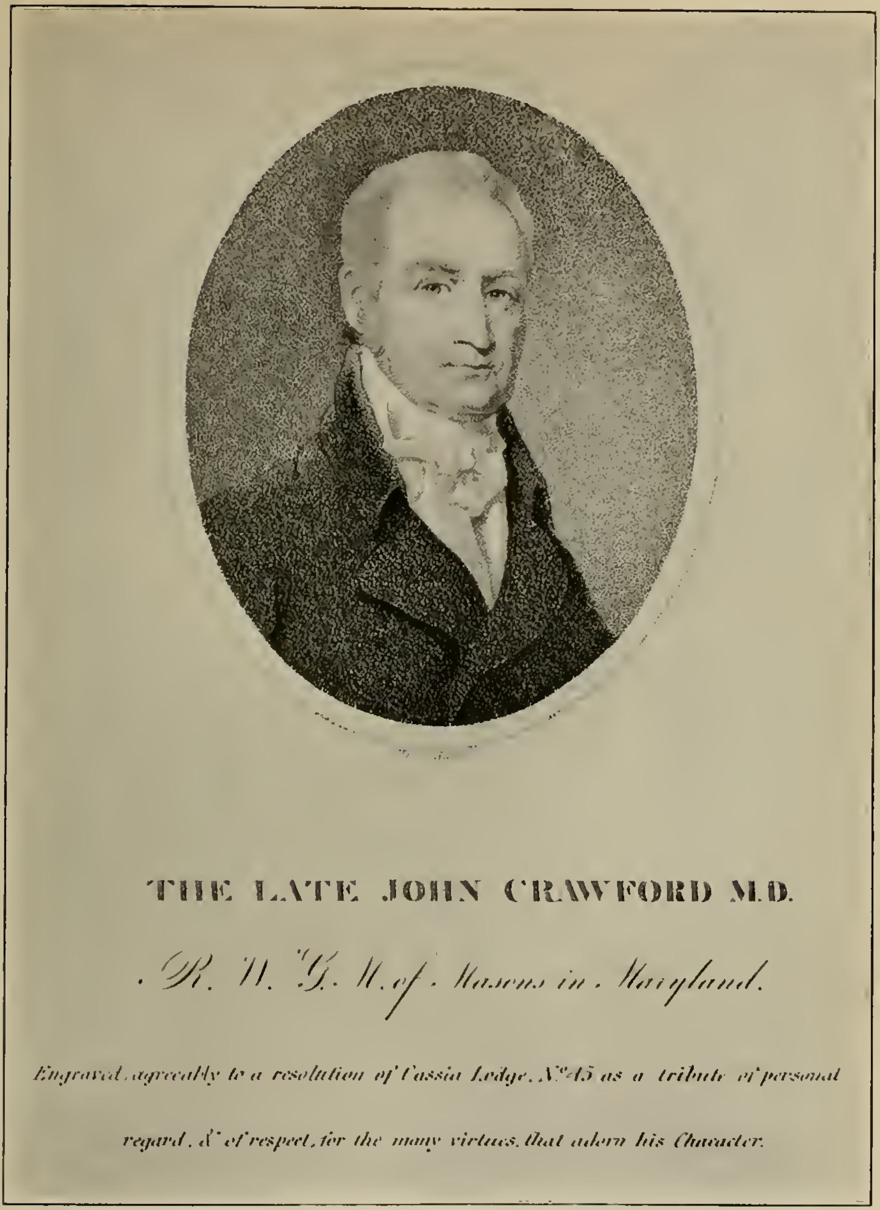
THE LATE JOHN CRAWFORD M.D.
R. W. G. M. of Masons in Maryland.
Engraved agreeably to a resolution of Cassia Lodge, N°. 45 as a tribute of personal
regard, & of respect, for the many virtues, that adorn his Character.

FIG. 1. The original of the above engraving of Dr. John Crawford was commissioned by the Cassia Lodge of the Masonic Order in 1814.

A British squadron of ten armed vessels was moving up Chesapeake Bay, and Baltimore was feverish with excitement The defenses of the city were being strengthened, in case an attack was made by the British fleet which now lay at the mouth of the Patapsco. On May 5 a report reached Baltimore "that the British were once more advancing to attack the city . . . . In the afternoon it was discovered that the alarm was a false one, and the soldiers were dismissed. An attack was still expected, however, . . . and work was actively continued . . . . for the special defenses of the city" (27). This accounts for the following entry in the Masonic Proceedings: "In consequence of the enemy having made some advances, and showing an indication to approach our river, the Grand Lodge did not meet till 9th inst" (28).

When the Grand Lodge met again it was to announce the death of their leader, a notice of which appeared in the *American and Commercial Daily Advertiser* on the following day, Monday, May 10 (1):

> Died yesterday morning at 10 o'clock, A.M. in the 68th year of his age, John Crawford, M.D., Right Worshipful Grand Master of Masons in Maryland.
>
> His name will constitute his eulogy.

The Masons conducted the funeral services of Dr. Crawford on Monday, May 10, 1813, when he was buried with all the ancient rites of the Order in the churchyard of Westminster Presbyterian Church on Fayette and Greene Streets . This piece of land, originally purchased from Col. John Eager Howard, was then the property of the First Presbyterian Church of which Crawford had been a communicant when he first came to Baltimore. There is a record that Crawford later transferred to the Second Presbyterian Church (14), on Baltimore and Lloyd Streets, that he purchased pew No. 150 on July 2, 1804, and that he was ordained an elder in April, 1811 (30).

It was the custom for the Masons to have their Annual Assembly and Feast on either of the St. John's Days. They decided to hold a memorial service for Dr. Crawford on the Feast Day of St. John the Baptist (June 24), and the following announcement was published on May 28 in the *American and Commercial Daily Advertiser* (2):

> GRAND LODGE OF MARYLAND
>
> Resolved that the R. W. Grand Master be requested to deliver an Eulogium on the character of our late Dr. John Crawford, on St. John's Day the 24th June, and the lodges as far as practicable, do appear and walk in procession to a church in this city. . . .
>
> By order, May 28th.

This notice was published every day until June 21, when a more explicit order was issued by the Masons to this effect (3):

GRAND MASONIC PROCESSION

The Brethren are desired to take notice that the Grand Lodge of Maryland will meet at Mr. Mallet's Assembly Room, in Charles st. at 10 o'clock precisely, on the 24th inst. and that the Procession will be formed at ½ past 10; to move down Baltimore st. to Gay street, along North Gay, to East street, and up East street, to the First Presbyterian Church.—Where an oration will be delivered by the R. W. Grand Master, in pursuance of a resolution of the Grand Lodge heretofore published.

Brethren, not members of any Lodge, as well strangers as residents, who may wish to join the procession, will have a station assigned them, by repairing to the room above mentioned at ¼ after 10.

The Medical and Chirurgical Faculty of Maryland and the Clergy of every denomination are respectfully invited to attend.

The citizens are respectfully requested to take notice, that the doors of the Church will be opened only for the admission of Ladies (for whom the Gallery will be exclusively appropriated) until the Procession shall have entered when they will be thrown open for the reception of all who can be accomodated.

By order,
Arch. Dobbin, G. S.

Consequently:

In obedience to a resolution of the R. W. Grand Lodge of Maryland passed at their May Session, directing that This Day should be set apart for the purpose of paying a last respectful homage to the memory of their late Grand Master JOHN CRAWFORD, M.D., the Masonic Brethren assembled at Mr. Mallet's Assembly Room in Charles-street, at 10 o'clock, where a procession was formed under the direction of the Grand Marshall, in the following order:

Subordinate Lodges according to juniority
Physicians and Clergy, two and two
A Band of Music
Grand Tyler with a drawn Sword
A Passed Master bearing the Standard
Members of the Grand Lodge, two and two
A Passed Master carrying the Green Light
Grand Chaplain
Three Passed Masters carrying three Golden Candles
Grand Secretary and Grand Treasurer with Rolls
Grand Wardens
Deputy Grand Master and Mayor of the City
R. W. Grand Master, supported by two Grand Deacons.

At half-past ten, the Procession moved down Baltimore-street to Gay-street, thence to East-street and along East-street to the First Presbyterian Church.

The front of the Procession having arrived at the door of the Church, halted; the ranks were opened and faced inwards and entered the Church in inverted order. As the Grand Master entered, Mr. Meinecke commenced a Voluntary on the Organ, which continued to be played until the Brethren were seated. The doors of the Church were then thrown open for the admission of the citizens, and the ceremonies of the day commenced by a prayer from the W. Grand Chaplain, after which an elegant anthem composed for the occasion by Mr. John Coale, was sung in full choir. Next followed the Eulogium on the character of Brother John Crawford, M.D. by Brother Tobias Watkins, M.D., R. W. Grand Master. (31.)

Dr. Watkins had at one time edited the *Baltimore Medical and Physical Recorder* during its brief period of existence in 1809. Dr. Crawford had been a large contributor to this medical journal and there can be no doubt that Dr. Watkins knew the background of his friend better, perhaps, than any other man in Baltimore. His address to the large congregation in the old First Presbyterian Church on East Street (now Fayette) was later published and printed in this city. It has been quoted by Cordell (9), Schultz (28), and Oliver (22), and is still the main source for all information regarding Crawford's life prior to 1796. The following facts from this eulogy pertinent to Crawford's personal life round out his portrait (31):

> Doctor John Crawford was the second son of a clergyman in the North of Ireland. . . . About the age of seventeen he was sent to the College of Dublin to commence his medical studies. How long he continued here is not certain. Most probably not very long; as he received his degree of Doctor of Medicine from the University of Leyden, at that time in high reputation. He afterwards made two voyages to the East Indies as Surgeon in the East India's Company's service. . . .
>
> From this time to the period of his marriage, which took place about the year 1778, no important particulars of his life have come to my knowledge. . . . Not long after his marriage, he was appointed Physician to the Hospital in Barbados, whither he went, with his family. . . .
>
> In 1782 the wretched state of his health, compelled him to return with his family to England. During this voyage a melancholy event occurred, which he never ceased to lament, the remainder of his days. His wife, to whom he was attached by every tie which can render the conjugal state delightful, died under an accumulation of mournful circumstances, and left him with two infant children. He proceeded on the voyage to England, where he remained until the recovery of his health, when he returned to Barbados. He removed not long after to Demerary, where he was appointed Physician to the Colony, by the Dutch Government, in whose possession it then was; and who conferred on him distinguished honors. . . .
>
> The public are already in possession of many of the fruits of his scientific researches; and much yet remains, entrusted to the care of one whose discriminatory mind, and whose friendship to the deceased author, will, I trust, not suffer him to withhold it long from the medical world. . . .
>
> Towards the latter end of the year, 1794, ill health again obliged the Doctor to seek relief in an European Climate. He went to England, and thence to Holland, for the purpose of arranging some affairs with the Government there. In the meantime the Colony of Demerary was transferred to the English; and at his return from Holland, he was offered the same appointment by the British Government, which he had held before under the Dutch, but the pressing solicitations of the late Mr. O'Donnell (his brother-in-law) to come to this Country, and the hope that accepting this invitation might prove advantageous to his children, induced him to decline his proposed reestablishment in Demerary; and to embark for the

> United States; which he did in 1796. From this period, it will hardly be necessary to dwell upon the incidents of his life. They must be known to most of those who hear me, as he came at once, and continued as a resident of this City. . . .
>
> He was deeply versed in all the learning of the Ancients; had a classical knowledge of the Latin and French languages; and could translate with sufficient facility the Greek and German. There was scarcely any author of celebrity either ancient or modern that he could not read. Physick and Divinity were his two favorite studies—but these did not occupy all his time. . . . History, philosophy, and most of the useful sciences engaged a portion of his attention; and for the two or three last years of his life, he devoted himself almost exclusively to the study of Natural History; or rather to the History of Animated Nature, . . . His . . . . object was to learn the customs, habits, and manners of the many interesting families of animals; . . . . In the year 1812, he was appointed, by the Regents of the Medical College of this State, LECTURER ON NATURAL HISTORY; and in pursuance of that appointment commenced a course of Lectures, which he was soon, however, compelled to abandon, for reasons not necessary to be noticed here.

When Dr. Crawford arrived in Baltimore in 1796 there were other learned men selecting this city for their practice. Dr. John Beale Davidge, from Ireland, and Dr. Nathaniel Potter, from the Eastern Shore, came that same year. Dr. Peter Chatard, formerly of San Domingo, came down from Wilmington, Delaware, where he had been practicing. Three years earlier Dr. Thomas Drysdale had arrived. Altogether there were about twenty-seven physicians in the city, which then had a population of 20,000 (25).

Medical activity in Baltimore had been progressing ever since Dr. Charles Frederick Wiesenthal of Revolutionary fame had spurred the profession to "regulate the practice of physic." The Medical Society of Baltimore (which was a forerunner of the Medical and Chirurgical Faculty of Maryland) had been reorganized by Dr. Wiesenthal's son in 1789. Young Dr. Andrew Wiesenthal had already started lecturing at his home on North Gay Street. Even while in London, where he studied anatomy under Sheldon and Cruikshank and listened to the lectures of the great Sir Percival Pott, Wiesenthal in a letter to his father, dated 1788, had outlined his future plans. "It is my intention when I return, to give a regular course of lectures on anatomy and to open a room for dissecting, in order that Baltimore may become better worth the while for students to come there, and to habituate myself to lecturing against some future period when proper arrangements and establishments may take place in the profession" (24). Dr. Wiesenthal lectured that first year on anatomy, physiology, pathology, operative surgery, and the gravid uterus. In 1790 he planned with Dr. George Buchanan to continue the lectures, hoping that "it may prove the beginning of a permanent Medical School." Dr. George Brown was to lecture on the practice of medicine; Dr. Lyde Goodwin on surgery; Dr. S. S. Coale on chemistry and materia medica; Dr. George Buchanan on midwifery; Dr. Andrew Wiesenthal on anatomy. All of these efforts were later embodied in lasting institutions which exist today — the Medical and Chirurgical Faculty of Maryland and the School of Medicine of the University of Maryland. Dr. Wiesenthal did not live to see either organization come into being, but died quite suddenly in December, 1798.

It is not unlikely that Dr. Crawford knew young Dr. Wiesenthal, for many of the latter's books came into the possession of the older man. Their signatures on the title page and their own individual bookplates, one superimposed upon the other, testify to their ownership. They had both been members of the same Masonic Lodge, Amicable No. 25. This fact together with their joint interests in medicine bespeak an acquaintance between the two men.

Dr. Crawford soon began to take more than just an active interest in the medical welfare of the city. In 1800 he submitted to the Baltimore City Council a report of local health conditions. This was done in conjunction with the Medical Faculty of Baltimore, of which he was chairman.[5] In the summer of 1800 Dr. Crawford procured a supply of virus from Dr. Ring in London and introduced vaccination in this section of the country at the same time that Dr. Benjamin Waterhouse was successfully applying the same procedure in Cambridge, Massachusetts. Dr. Waterhouse is generally spoken of as the man who introduced vaccination in the United States, because he advertised his success by sending letters to the editors of medical journals both in this country and abroad. Simultaneously Dr. Crawford ordered a new supply of vaccine from Dr. Ring in 1801, but he never published a paper on the subject. However, out of his efforts grew the Vaccine Institute—the first in America—established by Dr. James Smith in Baltimore in 1802. The contemporaneous use of vaccine by Waterhouse and Crawford has a curious analogy to the current controversy over the introduction of anesthesia in connection with surgery.

In 1801 the Baltimore General Dispensary was organized as a result of Dr. Crawford's efforts. He was one of the consulting physicians to the Baltimore Public Hospital, built in 1812, and held a similar honorary post in connection with the Board of Health. The Board of Health in those days consisted of several commissioners (civilians) who were appointed to a term of office. Crawford wrote to the Mayor in 1809 (5), suggesting that one of the commissioners be a physician, and asked to be considered for the post. It was not until

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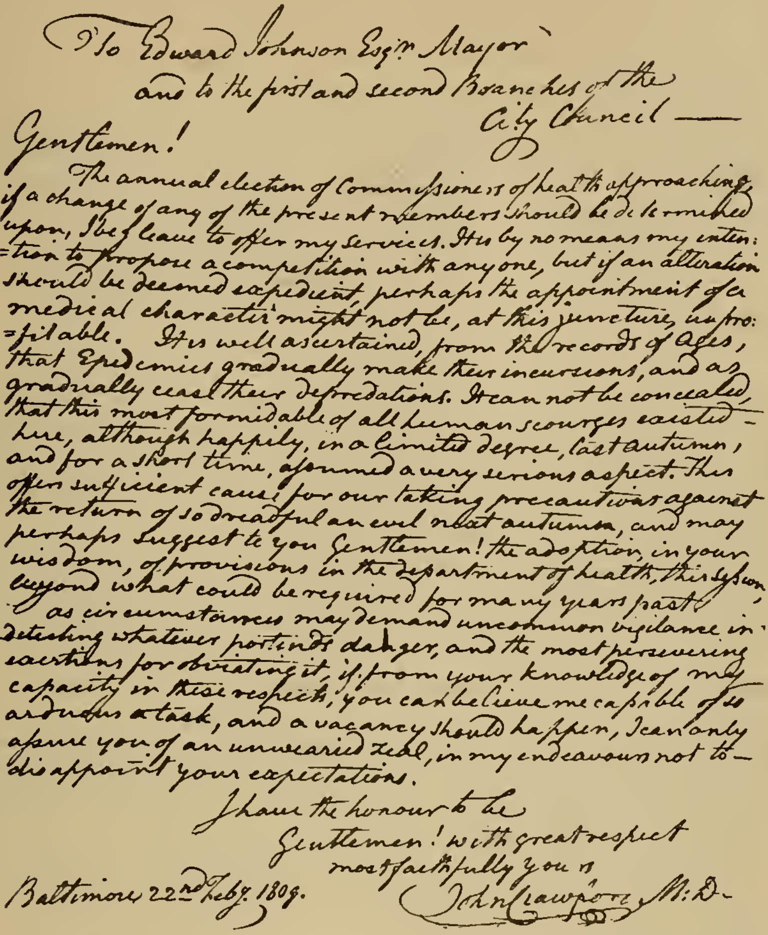
[5] Cited by Quinan and Cordell, but original sources discredit the statement.

1839, however, that a physician was made a member of the Board of Health Commissioners in Baltimore (25).



To Edward Johnson Esqr Mayor
and to the first and second Branches of the
City Council —

Gentlemen!

The annual election of Commissioners of health approaching, if a change of any of the present members should be determined upon, I beg leave to offer my services. It is by no means my intention to propose a competition with any one, but if an alteration should be deemed expedient, perhaps the appointment of a medical character might not be, at this juncture, unprofitable. It is well ascertained, from the records of Ages, that Epidemics gradually make their incursions, and as gradually cease their depredations. It can not be concealed, that this most formidable of all human scourges existed here, although happily, in a limited degree, last autumn, and for a short time, assumed a very serious aspect. This offers sufficient cause for our taking precautions against the return of so dreadful an evil next autumn, and may perhaps suggest to you Gentlemen! the adoption, in your wisdom, of provisions in the department of health, this season beyond what could be required for many years past; as circumstances may demand uncommon vigilance in detecting whatever portends danger, and the most persevering exertions for obviating it, if from your knowledge of my capacity in these respects, you can believe me capable of so arduous a task, and a vacancy should happen, I can only assure you of an unwearied zeal, in my endeavours not to disappoint your expectations.

I have the honour to be
Gentlemen! with great respect
most faithfully yours
John Crawford M:D.

Baltimore 22nd Feby 1809.

FIG. 2. Facsimile of Dr. Crawford's letter to the Mayor and City Council in 1809

To Edward Johnson, Esq. Mayor
And to the first & second Branches of the City Council

Gentlemen!

The annual election of commissioners of health approaching, if a change of any of the present members should be determined upon, I beg leave to offer my services. It is by no means my intention to propose a competition with anyone, but if an alteration should be deemed expedient, perhaps the appointment of a medical character might not be, at this juncture, unprofitable. It is well ascertained, from the records of ages, that Epidemics gradually make their incursions, and as gradually cease their depredations. It cannot be concealed, that this most formidable of all human scourges existed here, although happily, in a limited degree, last autumn, and for a short time, assumed a very serious aspect. This offers sufficient cause for our taking precautions against the return of so dreadful an evil next autumn, and may perhaps suggest to you Gentlemen! the adoption, in your wisdom, of provisions in the department of health, this session, beyond what could be required for many years past.

As circumstances may demand uncommon vigilance in detecting whatever portends danger, and the most persevering exertions for obviating it, if, from your knowledge of my capacities in these respects, you can believe me capable of so arduous a task, and a vacancy should happen, I can only assure you of an unwearied zeal, in my endeavors not to disappoint your expectations.

I have the honour to be
Gentlemen! with great respect
Most faithfully yours,

Baltimore, 22nd Feby. 1809.

John Crawford, M.D.

Dr. Crawford was not among the founders of the Medical and Chirurgical Faculty of Maryland, but shortly after that society was formed he became a member. Later he was censor and examiner for the Western Shore. In 1804 he shared with Dr. Davidge the honor of being orator at the June meeting.

"He was a participator, if not a leader, in most of the humanitarian enterprises of his day," states Dr. Cordell in his Memoir of John Crawford. "He was one of the founders and the most active member of the Maryland Society for Promoting Useful Knowledge, 1798 . . . . He was also connected with the Hibernian Benevolent Society from the earliest period of its existence and held several offices in it. To his indefatigable exertions, perhaps, more than to those of any other individual, is the State indebted for the establishment of the Penitentiary (1802). He was one of the founders of the Bible Society of Baltimore, an association of Christians of every denomination designed to promote the spread of the Gospel among all men. He was also one of the directors of the Baltimore Library, the first institution of the sort in the city" (9).

In spite of all the contacts that Crawford made in Baltimore and all the enterprising ventures which he inspired, he was never accepted among his medical contemporaries in the way that would have pleased him most. The local physicians did not agree with Crawford's theory of disease and this militated against his success in practice and teaching. Crawford had admitted this much to Benjamin Rush. It was not his lack of successful practice that disappointed him as much as it was the rejection of his teachings.

Crawford persisted, however, in expounding his theory of "animalculae." As early as 1790, when he was living in the Dutch West Indies, he had arrived at this idea of what is now known as "pathogenic organisms." He was convinced that the laws which govern the lower animals and the vegetable kingdom govern also the living germs which produce disease. He was familiar with Plenciz's (1705–1785) theory on contagium animatum. He was a great student of Linnaeus (1707–1778) who classified the micro-organisms. He constantly made marginal notes as he continued his reading of such scientists as Swammerdam (1637–1680) and Buffon (1707–1788). It was reasonable, therefore, that Crawford should begin his own course of lectures on the cause of disease in 1811 at his home on Hanover Street. In 1812 he was recognized by the Regents of the Medical College and was given a chair with the title of "Lecturer on Natural History." This course was abandoned shortly and no reason was ever given for its discontinuance.

Crawford, far in advance of his time, urged new ideas in the field of medicine before the profession was able or willing to put them into practice. When residing in Demerara he had formulated a proposition regarding a botanical garden, of which he wrote about 1795 in a paper entitled "A Letter Addressed to Lieutenant-General Mathew on the Means of Preventing, the Method of Treating and the Origin of the Diseases Most Prevalent and which Prove Most Destructive to the Natives of Cold Climates Visiting or Residing in Warm Countries."[6]

> I proposed to have the superintendence of the medical affairs of the colony of Demerary . . . confided to me, to have some lands which were the property of the States appropriated to the establishment of a Botanical Garden, wherein might be cultivated all the different plants, [which] I might learn from these country practitioners, were possessed of medical properties. That these should be cautiously brought into use and that specimens of such of these as were found to answer our expectations, with an account of their properties should be sent the Professor of Botany at Leyden, with the garden of which place Demerary should be affiliated and a correspondence with the professor enjoined.

Crawford was given assurance that these plans would be put into effect when "unhappily the revolution totally defeated this intention and it must be deferred until tranquility is restored."

Again in January, 1813 Dr. Crawford conceived an idea for a permanent board to examine medical appointments to the Army and Navy of the United States. In a memorandum to General William H. Winder, who was later to be in command of American troops opposing the British forces near Bladensburg, he outlined his plans (23):

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[6] MS is now in the possession of the Library of the Medical and Chirurgical Faculty of Maryland.

> Dear Sir:
>
> . . . Complaints have been made in the public papers of the insufficiency of the medical men employed in the Army. I *know* that the same cause of complaint exists in the Navy. When Mr. Smith was at the head of that department, I had some conversation and indeed wrote to him on the subject. I suggested the necessity of requiring that every surgeon and surgeon's mate should obtain from a competent authority, a testimonial of his being qualified for the office. This in Europe, is a sine qua non, the reasonableness of which cannot admit of a dispute. A suitable Board should be appointed for this purpose, and might serve for both land and sea departments. In such appointment, my experience assures me that a great improvement might be made on those of Europe. Instructions should be given that Board by which they should regulate their conduct. The Board should consist of not less than three—one for Anatomy and surgery, one for chymistry, and one for the Materia Medica, and the Practice in Diseases. . . .
>
> Encamping the soldiers is an object of such magnitude, that too much importance can not be attached to it. A well instructed Physician ought to know, almost to a certainty, the safety of the ground which may be chosen for this purpose. The difficulty of procuring ordinary medicines often occurs. A man sufficiently instructed, will often find such as are the most efficacious, in the woods and swamps where he sojourns.
>
> These my Dear Sir! are of so great moment as require only to be mentioned to evince their importance, and I could not go again to rest before I had submitted them to your consideration. This is my adopted country, and everything dear to it is dear to
>
> Your most affectionate humble servt.
> John Crawford
>
> Baltimore 16th Jany. . . .13.

Many of Crawford's ideas were put into practice before he died, but most of his theories were well ahead of his generation. His writings on the causes of disease were prophetic of discoveries to be made by Lister and Pasteur. He suggested that a physician be appointed to the Board of Health Commissioners in Baltimore but this was not heeded at the time. Dr. Crawford's plan for a permanent board to examine medical appointments in the Army and Navy was not realized until fifty years later. His efforts in the field of vaccination were never recognized until the credit had already been given to another. As is often the case, time has at last justified Dr. Crawford's theories and postulations, but the recognition which he so deeply coveted during his lifetime has gone to better known physicians or more widely published writers.

A bibliography of Crawford's writings, based on information by Cordell and Quinan, is given here in chronological and revised form:

"An Essay on the Nature, Cause and Cure of a Disease incident to the Liver Hitherto but Little Known, though very Frequent and Fatal in Hot Climates." George Kearsley, London, 1772.

"Observations on Native Camphor." Medical Commentaries. **8:** Second Decade, 253–266, 1794.

"Address Delivered at Grand Convention of Free Masons of the State of Maryland, on May 10th 1802, in Which Observance of Secrecy is Vindicated, and the Principal Objections of Prof. Robinson Against the Institution, Candidly Considered." Published for the benefit of the grand charity fund, Dobbin & Co., Baltimore, 1802.

"Dr. Crawford in Answer to Dr. Boissard on the Rise, Progress and Treatment of Yellow Fever." (Five letters) September 6, 8, 11, 14, and 25, 1802, in the Federal Gazette and Baltimore Daily Advertiser.

"Remarks on Quarantines, as Suggested by Dr. Caldwell's Oration." The Observer and Repertory of Original and Selected Essays [etc], **1:** and **2:** 1806–1807.

"An Extraordinary Case of Ascites." Baltimore Medical and Physical Recorder, **1:** 1–5, 1809.

"An Account of the Sanicula." Ibid., 222–231, 1809.

"A Case of Hepatic Affection." Ibid., 300–309, 1809.

"Observations of the Seats and Causes of Disease." Ibid., 40–52, 81–92, 206–221, 1809.

"A Lecture Introductory to a Course on the Causes and Seats of Diseases, Proposed to be Delivered in the City of Baltimore." Edward J. Coale, Baltimore, 1811.

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(23) OLIVER, JOHN RATHBONE: An Unpublished Autograph Letter from Dr. John Crawford (1746–1813) to General William Henry Winder. Bulletin of the Institute of the History of Medicine, **4:** 145, 1936.

(24) Old Maryland, Baltimore, **1:** 1905.

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(28) SCHULTZ, EDWARD T.: History of Freemasonry in Maryland. Mediary, Baltimore, **1:** and **2:** 1885.

(29) SMITH, R. W. INNES: English-speaking Students of Medicine at the University of Leyden. Oliver & Boyd, Edinburgh, 1932.

(30) WALKER, THOMAS H.: One Hundred Years of History—1802–1902, Second Presbyterian Church. Baltimore, Md., 1902.

(31) WATKINS, TOBIAS: Eulogium on the Character of Brother John Crawford, M.D. late R.W.G.M. of the Masons in Maryland, delivered in the First Presbyterian Church, on 24th June 1813, in obedience to a resolution of the R.W.G. Lodge of Maryland. By Bro. T. Watkins, M.D. Edward J. Coale, Baltimore, 1813.

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ITEMS

Dr. E. N. Boccanegra Lopez (U. of Md. 1916) has been appointed Adjunct Professor in the Department of Dermatology and Syphilology of the New York Polyclinic Medical School and Hospital.

Dr. Frank Greenwald (U. of Md. 1937) announces the opening of his office in Prattsville, N. Y., on July 1, 1940.

Dr. Gibson J. Wells (U. of Md. 1936) has opened an office at 100 East Twentieth Street, Baltimore, Md., for the practice of pediatrics.

OBITUARIES

Arnold, Charles Augustus, Pittsburgh, Pa.; B.M.C., class of 1902; aged 70; died, April 6, 1940, of coronary occlusion.

Aultz, Otis L., Charleston, W. Va.; P. & S., class of 1891; aged 71; died, May 14, 1940, of arteriosclerosis.

Bee, Isaiah E., Princeton, W. Va.; P. & S., class of 1890; died, March, 1940.

Berkley, Henry John, Baltimore, Md.; class of 1881; aged 79; died, April 5, 1940, of injuries received in a fall.

Bigelow, M. Willard, Payson, Utah; P. & S., class of 1911; aged 64; died, May 21, 1940, of angina pectoris.

Callen, J. Spencer, Shenandoah, Pa.; P. & S., class of 1881; aged 86; died, June 4, 1940.

Cobb, Ross B., Philadelphia, Pa.; class of 1913; aged 69; died, May 19, 1940, of chronic myocarditis.

Covington, Platt Walker, Salt Lake City, Utah; class of 1908; aged 55; died, April 20, 1940, of cerebral hemorrhage.

Devine, Harry L., Springfield, Mass.; B.M.C., class of 1909; aged 56; died, June 29, 1940, in the Wesson Memorial Hospital.

Doane, L. Leo, Highland Park, Ill.; P. & S., class of 1886; aged 83; died, April 11, 1940, of acute dilatation of the heart.

Eve, Robert C., Atlanta, Ga.; P. & S., class of 1892; aged 71; died, June 22, 1940, of carcinoma of the lung and myocarditis.

Foran, Michael J., Ithaca, N. Y.; B.M.C., class of 1902; aged 67; died, April 5, 1940, of myocarditis.

Foster, Henry Costello, Clear Spring, Md.; class of 1889; aged 72; died, April 29, 1940, in the University Hospital, Baltimore, of coronary thrombosis.

Gallagher, John H. C., Chicopee, Mass.; B.M.C., class of 1903; aged 59; died, March 19, 1940, at St. Petersburg, Fla., of a heart attack.

Garverich, Frank H., Harrisburg, Pa.; class of 1888; aged 78; died, June 15, 1940, of arteriosclerotic renal disease.

Gibbons, William H., Croom, Md.; B.M.C., class of 1884; aged 77; died, February 19, 1940, of myocarditis.

Hamilton, J. A., Decatur, Ohio; P. & S., class of 1883; aged 80; died, March 22, 1940, of heart disease.

Hardee, Parrott Rastus, Durham, N. C.; P. & S., class of 1885; aged 78; died, April 14, 1940, of bronchopneumonia and carcinoma of stomach with metastases.

Hardman, John Edward, Youngstown, Ohio; P. & S., class of 1909; aged 54; died, April 4, 1940, of nephritis and hypertension.

Jones, Casper Franklin, Baltimore, Md.; B.M.C., class of 1895; aged 76; died, May 27, 1940, of carcinoma of the prostate.

Ray, William Turner, Charlotte, N. C.; class of 1934; aged 37; died, June 16, 1940, of heart disease.

Rowland, Ernest, Liberty Grove, Md.; B.M.C., class of 1895; aged 65; died, April 27, 1940, of chronic myocarditis and nephritis.

Steinbeck, Karl, Parkersburg, W. Va.; P. & S., class of 1905; aged 58; died, April 20, 1940.

Ulfert, Carl William, Wheeling, W. Va.; P. & S., class of 1904; aged 58; died, June 30, 1940.

Wegefarth, George C., Baltimore, Md.; B.M.C., class of 1897; aged 64; died, March 22, 1940, of peritonitis.

Wheeler, Louis H., Tully, N. Y.; B.M.C., class of 1901; aged 62; died, May 15, 1940.

White, Benjamin Robert, Strasburg, Va.; class of 1896; aged 69; died, June 21, 1940.

White, Edward H., Cumberland, Md.; B.M.C., class of 1899; aged 70; died July 13, 1940 of a heart attack.

Wright, William Francis, Portsmouth, R. I.; B.M.C., class of 1908; aged 59; died, April 11, 1940, in Miami, Fla., of gastro-intestinal hemorrhage.

BULLETIN
OF THE
SCHOOL OF MEDICINE
UNIVERSITY OF MARYLAND

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REGIONAL GLANDULAR BIOPSY IN THE DIAGNOSIS OF BONE AND JOINT TUBERCULOSIS*†‡

MOSES GELLMAN, B.S., M.D.
BALTIMORE, MD.

The clinical pathology of orthopedic tuberculosis may simulate a variety of lesions, acute and chronic, presenting at times aspects so diverse as to defy clear-cut and definite differentiation. After all of the medical, surgical, radiological, biological, pathological, and bacteriological examinations have been made, a number of baffling cases still remain uncertainly diagnosed. Though late cases of tuberculosis of the joints, in which destruction has taken place, often offer comparatively little difficulty, according to Smith (1) not a few of these at operation prove to be some other entity. Frequently, only after the condition has been present for a long time is its true nature suspected. Early cases, that is, during the first year or two of the disease, are exceedingly difficult to diagnose and are the source of a high percentage of error.

Investigators in the past, having assembled large groups of material, found that the percentages of error in clinical diagnosis have ranged from 16 to 64 per cent [Sorrel (2) 31 per cent, Sundt (3) 33.9 per cent, Johannsen (4) 50 to 64 per cent, Milgram (5) 35 per cent, Smith (1) 10.0 per cent]. With a better understanding of the factors that entered into the misdiagnosis, with improvement in the thoroughness with which cases are being prepared, with an increased desire to establish more accurately the nature of the process under consideration, and with improvements in laboratory technic, these mistakes are gradually being reduced (6).

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* From the Department of Orthopedic Surgery, School of Medicine, University of Maryland, and the Kernan Hospital for Crippled Children.

† Preliminary Report read before the Medical Research Club, June 1, 1937.

‡ Received for publication November 29, 1940.

There is a general feeling, as expressed by Smith (1), that failure to recognize a tuberculous process is just as harmful as calling a benign lesion tuberculosis. It is difficult to decide which error causes the greater damage. In the first instance, delay in recognition seriously affects the health, permits increased bone and joint destruction, makes reparation difficult, and mitigates against the possibility of a more satisfactory end result. In the second instance, considering tuberculous an osteo-arthritis which actually is not tuberculous, subjects the patient to many years of unnecessary expense and anxiety. The parts are also subjected to prolonged immobilization, with the probability of final functional articular limitation. If misdirected surgical treatment is undertaken, irreparable ankylosis results. In addition, statistics purporting to evaluate the results of various forms of therapy are inaccurate and unreliable, unless definite proof of an acid-fast infection can be demonstrated. It, therefore, follows that efforts in every direction at the examiner's disposal should be utilized at the earliest moment to arrive at as positive a decision as can be determined.

The isolation of the organism is the only conclusive evidence that a given osteo-articular lesion is tuberculous (5). This does not always appear to be possible. The next best evidence is the discovery in pathological tissue of or connected with the lesions true tubercles of unimpeachable character. Aside from these methods, there are employed the following indirect means or diagnostic adjuncts: (1) *Clinical history*, embodying the development of the case as well as the presumptive value of contact with some form of tuberculosis. (2) *Physical examination* of the local condition, including heat, swelling, effusion, pain, spasm, limited motion, atrophy, abscess formation, not forgetting the existence of foci elsewhere in the body. (3) *Roentgenological examination* with the demonstration of decalcification, destruction, atrophy of the bone and soft parts, calcification of tubercles, unproductive osseous response. (4) *General biological reactions*, such as tuberculin tests with human and bovine material, used epidermally, intradermally and subcutaneously, and their local, focal and general responses, with the proper interpretations thereof. Other reactions, such as the sedimentation, complement fixation, agglutination and seroflocculation tests, opsonic index, and blood cultures have been used with uncertain success and are mentioned in passing.

More direct methods concern themselves with an attack upon the process itself or its products. Material obtained by aspiration, sinus currettages, and biopsy specimens are subjected to: (1) microscopic smear, (2) pathological section in the case of tissue, (3) culture, and (4) inoculation into guinea-pigs for the purpose of secondary recognition or recovery of the original organism.

As yet in some quarters there exists no unanimity of opinion as to the relative innocuousness of exploratory or diagnostic arthropsy. Girdlestone (7) and some of his colleagues feel that this procedure is not without hazard both to the patient and to the diagnosis. He cites the danger of postoperative sinuses (Osgood), the risk of advancement of the disease into the surrounding soft tissues (Ober), and the possibility of secondary pyogenic complications. False negatives are common reports from the histologist or bacteriologist, and guinea-pigs return a negative response if insufficient biopsy material is removed and if the intra-articular tissue, appearing pathological, is merely nonspecifically irritated as the result of a contiguous extra-articular process. Smith (1), on the other hand, thinks that in many cases an exploration offers the only means of making a positive diagnosis; that, if properly done, there should be no hesitation in resorting to this means which he regards as relatively innocuous. He feels it is justified by the extreme importance of being absolutely sure of the diagnosis before beginning treatment, no matter what the treatment may be. Girdlestone is willing to admit that arthropsy is free from peril if a positive diagnosis, made at the operating table or as soon thereafter as feasible, will be followed by an arthrodesis or fusion operation, but precarious when conservative treatment will be continued despite positive findings.

From the foregoing it is obvious that the problem of rendering a final decisive and correct verdict in all cases is not exactly a simple matter. Therefore, any safe and reasonable measure that can be added to those already in use should be given consideration. Such a method—that of regional glandular biopsy—was advocated by Ottolenghi (8) in 1933. This method appears to be a sensible supplement to those standard tests already employed while establishing the diagnosis of orthopedic tuberculosis. Before presenting this procedure in detail it will be helpful to discuss the reasoning that induced Ottolenghi to propose this particular idea.

Secondary adenopathy responding to an inflammatory or infective lesion is a common, everyday observation. If the lesion is external and severe enough, enlarged neighboring glands are sought for and easily found. Ottolenghi recognized the intimate association that exists between infection and the lymphatic-glandular reaction, and basing his reasoning on this relationship, felt that some information could be obtained from the nodes. His method consists of biopsy of the glands within the drainage range of the affected part. Whereas many observers for years noted the connection between the lymphatic-glandular system and tuberculosis, apparently no one before has advocated, as an aid in the diagnosis of bone and joint tuberculosis, the routine removal of regional glands, if easily available, and subjecting them to the same series of examinations accorded to material obtained elsewhere. In other conditions, such as Hodgkin's disease and neoplasm, studies have been made on the adenopathies present, a biopsy of which often provides important information. Basombrio (9) in 1931 published an important article on leprosy and its glandular responses. So impressed was Ottolenghi with Basombrio's principles that he was led to employ the same methods in dealing with tuberculosis. In addition, the tubercle bacillus appears to have a special predilection for lymphoid tissue, grows and reproduces rapidly in this medium. Calmette (10) affirms that the tuberculous cell is, in fact, a lymphoid cell. Every parenchymatous lesion is followed by a secondary adenopathy. For each tuberculous focus there is a corresponding specific lymph gland reaction. Do not the tracheobronchial nodes respond to pulmonary invasion? It is stated by Sergent (11) that there is no mediastinal adenopathy without a lung involvement. The mesenteric glands are constantly affected in intestinal tuberculosis. Sergent further contends that the adenopathy should be considered secondary to the initial tubercle, for the infection runs from the periphery to the glands and not vice versa. The glands, therefore, corresponding to the lymphatic territory of an osteo-articular tuberculosis, react the same way.

Objection may be raised that such nodes are primarily infected, but primary generalized tuberculosis of the glands as a systemic illness is very rare. It might be suggested that the demonstration of tubercle bacilli, or their typical recognizable tissue responses in the glands, does not prove that the lesions adjacent thereto are tuberculous. A lymphatic system that drains a positive focus which evokes a positive response in the focus' glands, while the opposite and control area produces a negative result, is reasonable evidence that the gland and lesion that match each other so perfectly must be intimately related.

The tubercle bacillus, then, after originally invading the bone, cartilage or lining of the joint, penetrates the leukocyte, invades the lymphatic efferent channels, is transported as far as the neighboring gland, and there renews or repeats the same pathological process. It is from the latter site or source that information is sought to explain what is going on in the nether or distal regions.

Lance (12) in an important work in 1919 called attention to the adenopathies secondary to tuberculosis of the bones and joints. He made a detailed study of their clinical character and indicated the location at which reactions are to be expected as they respond to various local sources. According to this author, enlargements are not necessarily an early sign but do become evident within a few months of illness. Girdlestone (7) found a gland in his neck seventeen weeks after accidentally implanting tubercle organisms in his finger during the course of an operation.

It is agreed that, in general, the intracapsular structures of the hip joint are drained by lymphatics which ultimately empty into glands situated within the pelvis. The deep and superficial inguinal glands to some extent assist in this drainage (Fig. 1c). The knee joint and lower leg lymphatics drain into the inguinal glands and, to a lesser degree, into the deep popliteal glands (Fig. 1b). The lymphatics of the fingers, hand, wrist and elbow drain into the supra-epitrochlear and axillary glands (Fig. 1a). The shoulder joint lymphatics drain into the axillary and sometimes into the supraclavicular glands. Therefore, for tuberculous disturbances in the lower extremities, the glands most commonly removed for examination are several of those situated at the inferior pole of Scarpa's triangle; for disturbances in the upper extremities, the glands most likely to be affected are the deeper axillary ones and the subclavicular group.

The adenopathies secondary to a peripheral tuberculous bone and joint process have especial but not striking characteristics. The glands are slightly enlarged if compared to those of the opposite side, one or two being larger than the rest; they are not tender, are firm, and exhibit only a mild periadenitic reaction. There is hardly anything macroscopically to distinguish them from their mates. The microscopic changes, however, according to Ottolenghi (8), fall into three groups:

"*First:* The most common finding is that of a typical tuberculous inflammation with the presence of tubercles. The giant cells have finely granular protoplasm, in the periphery of which are a series of nuclei arranged in the form of an arch, crown or horseshoe. Around the giant cells there is a thick layer of epithelioid cells with clear protoplasm and enlarged nuclei, then come lymphatic cells, deep in color, dense, with deeply stained nuclei. The number of tubercles need not be great and among them frequently are zones of glandular reaction without any specific character. The lesion gives the impression of being sluggish and attenuated in type. Very exceptionally spots of caseous necrosis and suppuration are observed (Fig. 2.)

"*Second:* In some cases the reaction is atypical. There are no giant cells but only areas abundant in epithelioid cells. This epithelioid reaction, though suggestive, does not justify a positive diagnosis which must await confirmation from guinea-pig or cultural tests from the specific glands under consideration.

"*Third:* In glands from old lesions, the fibrous tissue often engulfs the follicles so completely as to cause them to disappear, transforming the glands into true scar tissue so that there are residues of an inflammatory process whose specific characteristics cannot be demonstrated histologically. Sometimes the glands are even normal in appearance or at most show only a discrete inflammatory reaction. However, if the glands are macerated and routinely injected into guinea-pigs, tuberculous lesions and bacilli are often demonstrated in the autopsied animals."

Ghormley (13) reports that the mere presence of tubercles with giant cells cannot be taken as evidence of tuberculosis, as these tubercles on closer examination may be the result of a foreign body reaction. If, how-

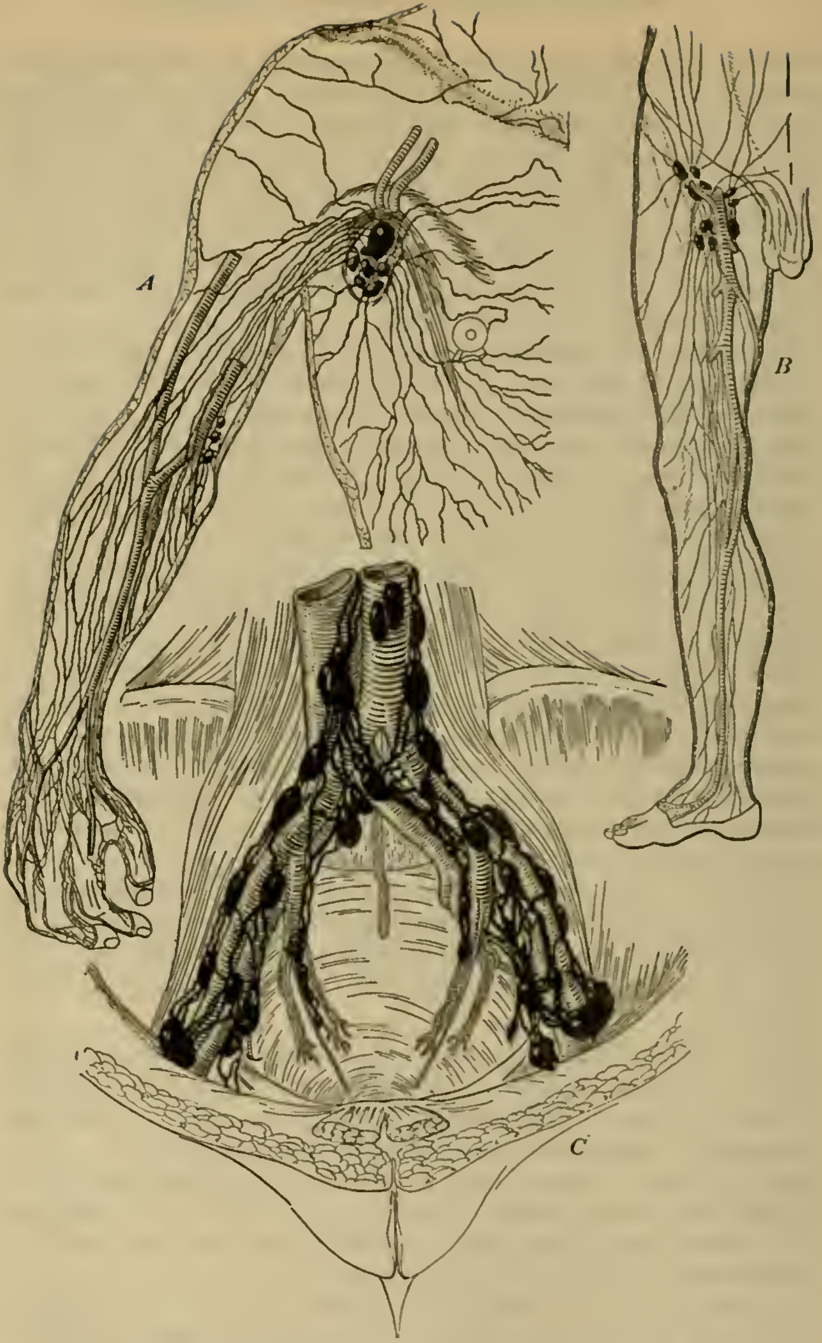

Fig. 1. *A*. Anatomical figure showing lymphatic drainage of upper extremity.
B. Anatomical figure showing lymphatic drainage of lower extremity.
C. Anatomical figure showing the intrapelvic lymphatic drainage of the hip joint.

ever, the tubercle is composed of typical epithelioid cells, with or without giant cells, and lymphocytes, the diagnosis of tuberculosis is justified.

The procedure of regional glandular biopsy is simple. Under local anesthesia the desired nodes are exposed, usually in the inguinal or axillary regions. After careful inspection and palpation two or more of the largest and firmest ones are selected and removed. One group is placed in a sterile container of normal salt solution and sent to the bacteriologic laboratory; another group is placed in formalin and sent to the pathologic laboratory. Thereafter, in the proper departments, the glands are subjected to (1) direct microscopic smear and staining for acid-fast bacilli, (2) culturing on suitable media, (3) maceration and inoculation into guinea-pigs intraperitoneally or subcutaneously into the groin, and (4) microscopic sectioning.

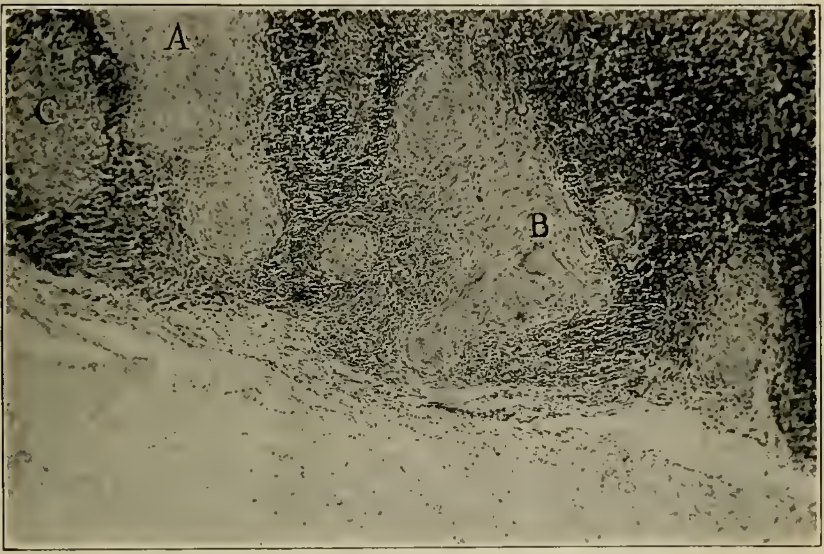

FIG. 2. Lymph gland showing conglomerate tubercles.
A, cellular tubercles; B, tubercle showing central caseation; C, germinal center.

Ottolenghi used the glandular biopsy in conjunction with other laboratory procedures in studying thirty-two cases, of which seventeen were considered as tuberculous. In the seventeen cases of proved tuberculosis, glandular biopsy either by culture, inoculation or microscopic section of the nodes was positive in fifteen cases or 88.2 per cent, whereas the diagnosis by direct biopsy, by culture, inoculation or microscopic section was positive in nine or 52.9 per cent of the cases.

Impressed by the valid reasoning underlying Ottolenghi's method, confirmation of this procedure was undertaken in 1936 in a group of cases in the Department of Orthopedic Surgery at the University Hospital and at the Kernan Hospital for Crippled Children. The active cooperation of the Department of Pathology of the University of Maryland and the Department of Bacteriology at the University Hospital has made the completion of this work possible.

This series at the present time consists of twenty-three cases. Sixteen of these patients had bone, joint or soft tissue lesions that were diagnosed as tuberculosis by the usual criteria. The remaining seven were known cases of nontuberculous conditions such as infectious arthritis, chronic osteomyelitis or chronic pyogenic arthritis. Thirty-four glandular biopsies were performed, fourteen unilateral, twenty bilateral. In many instances, therefore, glands were also removed from the opposite uninvolved sides as controls. In the nontuberculous group all cultural tests were negative and all pathological reports were negative except in one instance, that of a boy with recurrent synovitis of the knee observed over a period from 1936 to 1938 in which the impression from sections alone was possible tuberculous adenitis. In four of the tuberculous cases, glands were removed from the unaffected side as well. All four cases showed positive findings on the affected side, whereas none showed evidences of tuberculosis on the uninvolved or control side. In one tuberculous case (No. 11), glands were positive on both sides. The right extremity had a proved tuberculous knee; the left extremity had what was regarded as a skin tuberculid, which lesion, however, when excised and examined pathologically showed a nonspecific inflammation and scarring.

At the outset it must be stated that this procedure was not shown to be a satisfactory aid in cases of tuberculosis of the hip joint. There were five such cases in all, but in one (reported as "probable tuberculous adenitis") the excised inguinal glands showed no evidences of tuberculosis by any of the tests to which the specimens were subjected. This occurred in spite of the fact that in one case tubercle bacilli were recovered from the joint in pure culture by aspiration. In a second case, in which the glands were negative, a direct biopsy demonstrated undisputed evidences of the tuberculous nature of the process. These predominantly negative results were not to be unexpected since lymphatic drainage from the hip joint is primarily intrapelvic and inguinal only to a minor degree. This should not, however, act as a deterrent since there is always the probability of obtaining positive results.

There were twenty-one lesions in the sixteen tuberculous patients grouped as follows: foot—one, ankle—two, lower leg—two, knee—seven, hip—five, wrist—one, sternum—two, and rib—one. With the elimination of the five hip cases for reasons already stated, there remained sixteen glandular biopsies to be evaluated. Fourteen showed unequivocal evidences in the regional glands of a tuberculous process either by culture, guinea-pig inoculation or on microscopic sectioning. In one case the pathological report was probable tuberculous adenitis, but from biopsy material of the patient's knee joint tubercle bacilli were recovered by culture and guinea-pig inoculation. This would bring the total of positive results to fifteen out of sixteen, or 93.75 per cent. The only case that was reported as negative had just one gland removed from the axilla by a member of the intern staff and pathological section was the sole test to which this gland was subjected. This particular patient was virtually riddled with tuberculosis (jaw, thumb, rib, spine, and lungs). It is just as well that the result was negative for this would serve to refute the contention that general glandular tuberculosis is not to be unexpected in a patient affected with so many foci.

Some criticism may be leveled at the paucity of positive cultures (as seen on chart) in glands that were pathologically positive. Since the Kernan Hospital is located in the suburbs of Baltimore and the glands had to be transported a long distance to the University of Maryland Hospital laboratories, and, since at times an unavoidable or unnecessary delay prevented the glands from reaching the laboratory in the proper time, the chances of positive cultures could have been lost.

CASE REPORTS

Several of the cases are of particular interest and warrant special consideration. The following one is cited to give credence to the contention that the regional glands are capable of harboring the organism of the lesion distal to them:

P. J., a 13 year old colored girl, was seen at the Johns Hopkins Hospital dispensary several days after a puncture wound in the region of the left knee. She had all the clinical and laboratory evidences of an acute pyogenic arthritis. The knee was drained. At first, colon bacilli were cultured, later, unidentified gram-negative bacilli. After the acute symptoms subsided she was admitted to the Kernan Hospital. The knee, though closed, failed to regain its normal appearance and function but looked rather like a subacute chronic arthritic condition. Repeated aspirations and cultures of the joint fluid produced the gram-negative bacilli. From the inguinal glands on the involved left side the same gram-negative rods were isolated, whereas cultures of right inguinal glands were always sterile.

In this case regional glandular biopsy demonstrated the true nature of the disease long before convincing clinical and roentgen evidence confirmed the positive gland findings:

Case no. 6: C. R., a white boy, age 5, was admitted to the Kernan Hospital on April 26, 1934, with a preliminary diagnosis of tuberculosis of the right knee. This diagnosis was changed to syphilitic synovitis on the strength of a positive Wassermann test and negative results from culture and guinea-pig injection of material aspirated from the joint.

SUMMARY OF IMPORTANT DATA IN TUBERCULOUS CASES

CASE HISTORY	NAME	AGE	COLOR	CLINICAL DIAGNOSIS	X-RAY DIAGNOSIS	EXAMINATION OF ASPIRATIONS			DIRECT BIOPSY				GLAND BIOPSY					TUBERCULIN	WASSERMANN	FINAL DIAGNOSIS	REMARKS
						Smear	Culture	Guinea-pig	Smear	Culture	Guinea-pig	Pathology	Side	Smear	Culture	Guinea-pig	Pathology				
1	M. J. P.	3	W	Tbc. ankle l.	Tbc. ankle l.	—	—	—	—	—	—	Tuberculosis	L I	—	—	—	Tuberculosis	Pos.	Neg.	Tuberculosis, ankle, l.	Died of tuberculous meningitis.
													R I	—	—	—					
2	D. J.	4	C	Tbc. rt. knee	Tbc. knee, rt.	—	—	—	—	—	—	—	L I	—	—	—	Tuberculosis	—	Neg.	Tuberculosis, knee, rt.	Transferred to sanatorium.
				Tbc. pulmonary	Tbc. pulmonary								R I	—	—	—				Pulmonary tuberculosis	
3	B. B.	7	C	Tbc. knee, rt.	Tbc. knee, rt.	—	—	—	—	—	—	Tuberculosis	L I	—	—	—	Tuberculosis	Pos.	Neg.	Tuberculosis, knee, rt.	Arthrodesis, result, good.
													R I	—	—	—					
4	D. M.	3	C	Tbc. knee, l.	Tbc. knee, l.	Neg.	Neg.	Neg.	—	—	—	Neg. for tbc.	L I	—	—	Neg.	Tuberculosis	Pos.	Pos.	?	Seems well, noted in text.
				Granulations	L.	—	—	—	—	Neg.	Neg.	Prob. tbc.	R I	—	—	Neg.	Hyperplastic adenitis			Normal knee, rt.	
				Normal knee, rt.	Normal knee, rt.																
5	S. B.	5	C	Tbc. spine	Tbc. spine	—	—	—	—	—	—	—	L I	—	—	—	—	—	Neg.	Tuberculosis, spine	Nonoperative fusion.
				Tbc. hip, rt.	Tbc. hip, rt.								R I	—	—		Probable tbc.			Tuberculosis, hip, rt.	Arthrodesis, result, good.
				Tbc. sternum	Tbc. osteitis								L A	—	—	—	—			Tuberculosis, sternum	Excision of diseased bone, result, good.
													R A	—	Pos.	Neg.	Probable tbc.				

6	C. R.	5	W	Syphilis or osteo-arthritis		—	Neg.	Neg.	—	—	—	—	L I	—	Neg.	—	Tuberculosis	Pos.	Pos.	Tuberculosis, knee, l.	Extensive destruction knee, l.
				Tbc. knee, l.	Nontbc.								R I	—	Neg.	Neg.	Hyperplastic adenitis				
7	J. M.	4	W	Tbc. hip, l.	Tbc. hip, l.	Pos.	Pos.	—	—	—	—	—	L I	Neg.	Neg.	Neg.	Hyperplastic adenitis	—	Neg.	Tuberculosis, knee, l.	Conservative treatment; does fairly well with two stiff hips.
				Tbc. hip, rt.	Tbc. hip, rt.	Neg.	Neg.	—	—	—	—	—	R I	Neg.	Neg.	Neg.	Hyperplastic adenitis			Tuberculosis, knee, rt.	
8	R. J.	12	C	Tbc. foot, l.	Tbc. foot, l.	—	—	—	—	—	—	—	L I	—	—	—	Tuberculosis	—	Neg.	Tuberculosis, tarsus, l.	Conservative treatment, result, good.
													R I	—	—	—	—				
9	D. R.	2	W	Tbc. hip, l.	Tbc. hip, l.	—	—	—	—	—	—	—	L I	Neg.	Neg.	Neg.	Hyperplastic adenitis	Pos.	Neg.	Tuberculosis, hip, l.	Also congenital syphilis.
													R I	Neg.	Neg.	Neg.	Hyperplastic adenitis				
10	E. R.	9	W	Tbc. hip, rt.	Tbc. hip, rt.	—	—	—	—	—	—	Tuberculosis	L I	Neg.	Neg.	Neg.	Hyperplastic adenitis	Pos.	Neg.	Tuberculosis, hip, rt.	Arthrodesis, result, good.
													R I	Neg.	Neg.	Neg.	Hyperplastic adenitis				
11	J. D.	1⅓	W	?Tbc. knee, rt.	Chronic synovitis	Neg.	Pos.	—	—	—	—	Prob. tbc.	L I	Neg.	Neg.	—	Tuberculosis	Pos.	Neg.	Tuberculosis, knee, rt.	Arthrodesis, result, good; tuberculid? thigh, l.
													R I	Neg.	Neg.	—	Tuberculosis				
12	E. P.	5	C	Tbc. soft tissues about l. ankle	Negative	—	—	—	Neg.	Neg.	Pos.	Tuberculosis	L I	Neg.	Pos.	Pos.	Tuberculosis	Pos.	Neg.	Tuberculosis, soft tissues about left ankle	Excision, final result not known.
													R I	Neg.	Neg.	—	Neg.				

SUMMARY OF IMPORTANT DATA IN TUBERCULOUS CASES—*Concluded*

CASE HISTORY	NAME	AGE	COLOR	CLINICAL DIAGNOSIS	X-RAY DIAGNOSIS	EXAMINATION OF ASPIRATIONS			DIRECT BIOPSY				GLAND BIOPSY					TUBERCULIN	WASSERMANN	FINAL DIAGNOSIS	REMARKS
						Smear	Culture	Guinea pig	Smear	Culture	Guinea pig	Pathology	Side	Smear	Culture	Guinea pig	Pathology				
13	G. A.	6	C	Tbc. soft tissues of r. lower leg		Pos.	—	—	—	—	—	—	L I	Neg.	—	Neg.	Neg.	Pos.	Neg.		Pulmonary tuberculosis.
				Tbc. hand, rt.	Tbc. hand, rt.	Pos.	—	—	—	—	—	—	R I	Pos.	—	Pos.	Tuberculosis			Tuberculosis, hand, rt.	
				Tbc. rib, rt.	Tbc. rib, rt.	Neg.	Pos.	—	—	—	—	—	L A	—	—	—	—			Tuberculosis, rib, rt.	
				Tbc. jaw Tbc. spine	Tbc. jaw Tbc. spine	Pos.	—	—	—	—	—	—	R A	—	—	—	Neg.			Tuberculosis jaw Tuberculosis spine	Spine fusion.
14	H. B.	13	C	Tbc. sternum	Tbc. sternum	—	—	—	—	—	—	Tuberculosis	L A	—	—	—	—	Pos.	Neg.	Tuberculosis sternum	Cured by excision of diseased tissues.
													R A	—	—	—	Tuberculosis				
15	W. W.	19	C	Tbc. knee, rt.	Tbc. knee, rt.	—	Pos.	—	—	—	—	—	L I	—	—	—	—	—	Neg.	Tuberculosis knee, rt.	Tuberculosis of mediastinum?
				Tbc. wrist, rt	G.C. wrist, rt.							Tuberculosis	R I	—	Pos.	Pos.	Tuberculosis			Tuberculosis wrist, rt.	
													L E	—	—	—					
													R E	—	Pos.	Pos.	Tuberculosis				
16	F. J.	3	C	Tbc. knee, l.	Tbc., synovitis knee, left	—	Neg.	—	—	Pos.	Pos.	Tuberculosis	L I	—	—	—	Probable tbc.	Pos.	Neg.	Tuberculosis, knee, l.	Arthrodesis, result, good.
													R I	—	—	—					

—, test not done or not recorded.

LI, left inguinal gland; RI, right inguinal gland; LA, left axillary gland; RA, right axillary gland; LE, left epitrochlear gland; RE, right epitrochlear gland; Neg., negative for tuberculosis Pos., positive for tuberculosis.

The patient received antiluetic treatment, was fitted with a protective knee brace, and allowed to become ambulatory. On August 23, 1936 a right inguinal gland biopsy showed definite evidences of tuberculosis. Roentgenograms on May 24, 1937 revealed marked bony destruction, and the changes were readily recognized as tuberculous in nature.

There is one final case that has proved somewhat disconcerting, yet it is by far the most interesting one in the entire series:

Case no. 4: D. M., a colored girl 3 years old, was admitted to the Kernan Hospital on April 20, 1936, with a history of swelling of the left knee of two years' duration. The tentative diagnosis was tuberculosis. The results of aspiration and culture were negative. A left inguinal gland biopsy on May 1, 1936 was reported as tuberculous adenitis; a right inguinal gland biopsy on October 12, 1936 was reported as hyperplastic adenitis, nonspecific. The serologic test for syphilis was positive. She received regular antisyphilitic treatment. While wearing a cast, a draining sinus developed which finally closed after several months. On May 21, 1937 the left knee was widely explored. The cartilage of the femur and tibia was normal in appearance. Although the synovial tissues were thickened, there were no evidences of tuberculosis observed in situ or on pathological section. Culture and guinea-pig tests were negative. The knee joint seemed to be doing well, so on the strength of the negative reports the patient was allowed to walk freely about the wards. Two-and-one-half months later she fell and sustained a supracondylar greenstick fracture of the left femur. While lying in bed in traction, without warning and rather suddenly, the entire arthropsy incision, long since healed by primary intention, spontaneously opened down to the joint. The margins of the wound appeared thickened, grayish and necrotic. A biopsy made from this dirty-looking material was reported as probably tuberculous granulation tissue. Under no particular treatment other than cleanliness and rest, in the same mysterious manner that prompted the dissolution of the wound, the area healed promptly and has remained healed ever since. The knee is slightly thickened and crepitant, the motions remain excellent, and the child has as yet had no further difficulty. In spite of continued antisyphilitic therapy over a long period of time, the Wassermann is still positive.

SUMMARY

There has been presented a series of twenty-three cases of bone and joint disease in which thirty-four regional glandular biopsies were performed. Seven cases were nontuberculous, and in six of these the glands were entirely negative to all the tests to which the specimens were subjected. In one of these cases the pathological diagnosis was "possible" tuberculous adenitis. In the remaining sixteen cases of proved tuberculous etiology in which sixteen lesions were under consideration, the glandular biopsy test was positive in fifteen or 93.75%.

CONCLUSIONS

Regional glandular biopsy in a limited number of bone and joint cases has been found to be a valuable diagnostic aid. It has been especially useful in osteo-articular tuberculosis. It has corroborated other positive findings and in some instances has been the only positive element, in others the only material available. These glands, coming within the drainage range of the initial process, may be regarded as a component of the primary focus. Regional glandular biopsy compares more than favorably with direct arthropsy and is superior to an incomplete exploration. It can be employed in those cases where direct biopsy is refused or interdicted. The technic is simple, the procedure harmless. There are no contraindications to it. It is free from the dangers and errors of exploration. There have been no sinus aftermaths. The wounds have healed without extension of infection to the surrounding tissues. The glands are subjected to the same routine tests as material obtained by other methods. Lesions of the hip joint give the most uncertain results.

While present experience may not warrant the suggestion that this method replace diagnostic arthropsy, it should take precedence over direct biopsy when conservative treatment is to be continued in the face of positive findings revealed by exploration, reserving the latter procedure to those instances in which radical surgery is contemplated in the event tuberculosis is found. Although this method has thus far been most helpful and convincing, the small number of cases would not embolden one to suggest that it replace any of the standard tests now employed. It is a valuable adjunct. Further and more extensive observations by interested colleagues will define more clearly the possibilities of regional glandular biopsy and will serve to confirm or deny the conclusions that have been drawn from its use as herewith presented.

Grateful appreciation is expressed to the Department of Pathology of the School of Medicine, University of Maryland, and to the Department of Bacteriology of the University Hospital for their many courtesies during the preparation of this work.

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GAS GANGRENE*†

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In 1846 Velpeau (1) wrote "The emphysema which is sometimes added to the complications of fractures even from the first day and before the appearance of any symptoms of gangrene or inflammation, is one of those accidents, which, under such circumstances, must emphatically indicate amputation. Though no person has hitherto pointed it out, I have noticed it in six cases and three out of five, in whom the leg was the seat of the disease, died." There has been but little change in attitude toward this disease during the past one hundred years. Moreover, the mortality statistics appear to be much the same now as then.

In 1877 Pasteur described Bacillus vibrion septique as being implicated in the condition. In 1892 Welch and Nuttall and, in the same year, Fränkel described the bacillus which has since become known as B. welchii and has been found to predominate in such infections. In 1894 Novy described the bacillus which has come to bear his name, or which is better known as B. oedematiens. Many other bacilli of the gas forming group have since been described and implicated in the pathogenesis of gas gangrene. Little further progress was made in the treatment of the disease, however, until the World War, at which time intensive studies were made. In 1914 the incidence of occurrence of gas gangrene in the wounds was estimated at 12 per cent, with a mortality of 20 to 25 per cent. By 1918, as a result of better organization, the incidence had dropped to 1 per cent. The report of the Surgeon General of the United States Army (2) following the war called attention to symbiotic activity of the anaerobic gas forming organism and the aerobic streptococci, staphylococci.

The bacteriology, mechanism of infection, and other characteristics, are well known in gas gangrene. The symptom complex which has come to be associated with it is likewise well known but not always appreciated in the individual case. Callender in his article (3) states that most cases are found about four days after the actual onset of the disease. He stresses the importance of local wound inspection and immediate culture from the depths of the wound on the slightest suspicion as the most important lesson learned from the review of 109 cases. The mortality statistics in most series are placed at from 10 to 40 per cent. In Callender's series it was 51 per cent.

There appears to have been a gradual evolution in the treatment of gas

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* From the Department of Surgery of the Baltimore City Hospitals.

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gangrene but there still seems to be no unanimity of opinion in this regard. The prophylactic antitoxin which has become a routine procedure in nearly all hospitals has not proved its worth. The use of therapeutic doses of antitoxin is also of debatable value. Bates (4) reported sixteen cases treated with and sixteen cases treated without antiserum. The mortality in the former group was 18 per cent and in the latter 50 per cent. Eliason (5), basing his conclusions on collected cases, stated that antiserum with conservative surgery, that is, local debridement with incision of gangrenous areas, was the method of choice as opposed to amputation. In this article the patients were divided into three different groups. Those in group I did not receive therapeutic doses of sulfanilamide. In group II sulfanilamide was administered by mouth in therapeutic quantities. Those in group III had large amounts of sulfanilamide implanted in the wound and in many cases were given large doses orally.

GROUP I

The following four cases were treated in the same manner prescribed by Eliason. The third case was apparently of such a malignant nature that little other than local treatment was instituted.

Case No. 1: W. J., a 26 year old colored male, was admitted with a compound fracture of the femur. The leg was cleansed and the patient given routine antigas* and antitetanus toxins.** Four days after admission symptoms suggested and cultures proved gas gangrene. The patient died a short time after a guillotine amputation.

Case No. 2: W. H., was a 6 year old boy who had struck his head on a rusty projecting rod. There was no evidence of deep injury so the wound was closed loosely around small gutta-percha drains. The patient was given routine antitetanus serum and sent home. Two days later there were signs of meningismus and localized abscess. Operation proved this; however, the patient died subsequently. He was given routine antigas, antitetanus sera, and sulfanilamide after admission to the hospital, but obviously these were administered too late in his illness. Cultures were positive for gas forming bacilli.

Case No. 3: W. M., a 33 year old white male, was referred from another hospital where a compound fracture of the tibia and fibula had been reduced and a laceration of the left leg sutured. Examination revealed considerable maceration of muscle which it was felt justified further debridement and drainage. On the second day following the injury there was evidence of gas bacillus infection. Treatment consisted of continuous irrigations and debridement each day. The patient was given antigas and antitetanus sera (routine), and sulfanilamide therapy was begun when the gas was discovered. He was given only 20 grains every six hours. The patient died six days after the accident and four days after the finding of the gas.

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* One ampule of routine antigas serum contains:
10,000 units of B. perfringens (welchii)
10,000 units of B. vibrion septique
200 units of B. sordellii
2,500 units of B. histolyticus
1,000 units of B. oedematiens

** Routine antitetanus serum contains 1,500 units.

Case No. 4: M. B., a 31 year old negress, was admitted with multiple simple fractures after jumping out of a third story window. The patient was kept quiet for a few days and then taken to the operating room for a resection of the head of the radius and a repair of the left patella. Two days after the operation, gas was escaping from the incision. The arm and forearm were opened and the patient put on prontylin, but she did not receive antigas serum. Death occurred the next morning.

It will be noted that the first two cases were given prophylactic antitoxin. In the latter two it was obviously given too late in the course of the disease to be of any prophylactic value and the dosage prescribed was too small for therapeutic value. Three of the cases were treated with debridement, the fourth with amputation of the diseased extremity. All died. It may be stated fairly that the debridement and amputation represent the major part of the treatment.

Bohlman (6) in 1937 reported three cases treated with sulfanilamide by mouth, with excellent results. The following three cases were treated in a similar manner.

GROUP II

Case No. 5: A. Z., a 43 year old white male, suffered compound fractures of both lower legs. He was given a transfusion and intravenous fluids to combat shock. Later the legs were cleansed and debrided, fractures reduced, and casts applied. Routine antigas and antitetanus sera were given on admission. The next night, while the patient was irrational, he removed the cast from the right leg. On the second hospital day the right leg was disarticulated at the knee joint because of gas gangrene and poor circulation. The patient was given several transfusions and the stump treated with Dakin's solution and magnesium sulphate compresses. Eight days after the accident, gas was found in the other leg and it was therefore Dakinized. Sulfanilamide was started, 20 grains every four hours, two days after admission and continued for three months, when it was discontinued because of agranulocytosis. He was given twelve transfusions totaling 4350 cc., and routine ampules of antigas serum. The gas infection in the right leg cleared up, as did a secondary infection, therefore a reamputation could be performed later. Subsequently a Roger-Anderson reduction was done on the left leg. After three months, infection appeared around the pins and they had to be removed and a walking cast applied. The patient was discharged from the hospital approximately seven-and-one-half months after admission.

Case No. 6: J. L., a 47 year old white male, was admitted with a compound fracture of the left femur, after being treated for shock and after receiving routine antigas and antitetanus sera at another hospital. The wound was thoroughly cleansed and left open. Sulfanilamide therapy was begun immediately with an initial dose of 90 grams, followed by doses of 15 grains every four hours. Four days later gas gangrene was obvious. Since the blood sulfanilamide level was only 4.5 mg. % at this time, he was given 20 grains every hour for six doses, and thereafter 20 grains every four hours. That same afternoon the blood level was 10 mg. %. Later in the evening there was still some bubbling from the wound but it was much less than it had been in the morning and the odor was not as noticeable. From then on his course was quite satisfactory. Sulfanilamide was discontinued after twenty-eight days because of a skin rash, but the patient still had some infection in the site of the fracture.

Case No. 7: A. D., a 42 year old male negro, sustained a compound fracture of the radius and ulna. The wound was cleansed, the fracture reduced, and a cast applied. The patient was given routine antigas and antitetanus sera, and sulfanilamide therapy was begun with doses of 20 grains every four hours. Forty-eight hours after admission definite gas bacillus infection was present, with crepitation extending almost to the shoulder. After a guillotine amputation of the hand, multiple incisions were made in the arm and the wound Dakinized. At this time the blood sulfanilamide level was only 1.5 mg. % so the patient was given 80 grains immediately and 30 grains every four hours. The next day the blood level was 9 mg. % and the "mousey" smell had practically disappeared. Five days after the amputation the gas was all out of the arm and maggots were put in the wound to clean up the destroyed tissue. Two months after admission a B. pyocyaneus osteomyelitis was found around the radius and ulna. These bones were disarticulated at the elbow joint and the arm healed promptly. The patient was discharged approximately three months after admission. He received a total of 600 cc. of blood and 2 ampules of routine antigas serum. Sulfanilamide was continued in gradually decreasing doses for forty-two days. Smear and cultures were positive for B. welchii.

All three patients recovered. The usual doses of prophylactic antisera were given and gas gangrene developed in each case after the administration of antisera. All received large prolonged amounts of sulfanilamide. The first patient developed agranulocytosis and it was necessary to transfuse him frequently. In the third case, the emphysema had progressed to the axilla before the infection was noted. The temperature and pulse were normal. Recently all compound fractures have been placed on prophylactic dosages of sulfanilamide, with an initial dose of 80 grains followed by 20 grains every four hours. It may be worth while to suggest that patients under this regime may fail to give the usual systemic indications of gas bacillus infection which is expected. Therefore, all compound fractures and deep lacerations must be watched very carefully for the local evidence of infection, as there may be no general manifestations as are so often described in gas bacillus infection. This case also was interesting in respect to the rôle played by maggots in the treatment. By their use it was unnecessary to decide at what level to debride the arm and it was thus possible to avoid the risk of opening up the lymphatics to the ever-present streptococci and staphylococci.

In 1939 Jenson, Jahnsrud and Nelson (7) reported the prophylactic implantation of sulfanilamide locally into dirty lacerations and compound fractures. They employed primary closure of all such wounds where possible. This procedure was followed in the following representative cases.

SUMMARY OF CASES

	CASE	INJURY	SURGICAL PROCEDURE	ANTISERA	SULFANILAMIDE				RESULTS—COMPLICATIONS
					In wound	By mouth	Duration	Blood level	
1	W. J.	Compound fracture of femur	Cleansed, later amputation	*Antigas *Antitetanus	0	0	0	0	Developed gas gangrene, fatal in four days.
2	W. H.	Penetrating wound of skull and brain	Cleansed and sutured, later drained	Antigas Antitetanus	0	0	0	0	Developed gas gangrene, fatal.
3	W. M.	Laceration of left leg	Debridement and irrigation	Antigas Antitetanus	0	20 gr. q. 6 h.	4 days	?	Developed gas gangrene, fatal in four days.
4	M. B.	Resection of head of radius	Incision opened	0	0	30 gr.	Few hours	?	Developed gas gangrene, fatal in few hours.
5	A. Z.	Compound fractures of both lower legs	Cleansed, debrided, later amputation, right	Antigas (6 ampules) Antitetanus	0	20 gr. q. 4 h.	3 months	?	Developed gas gangrene, patient living.
6	J. L.	Compound fracture of left femur	Opened and cleansed	Antigas and Antitetanus	0	Initial 90 gr.; 15 gr. q. 4 h.	28 days	10 mg. %	Developed gas gangrene, leg still draining.
7	A. D.	Compound fracture of radius and ulna	Cleansed, debrided, later amputation. Dakinized	Antigas (2 ampules) Antitetanus	0	20 gr. q. 4 h.; later—initial 80 gr., 30 gr. q. 4 h.	10 days	1.5 mg. % 9 mg. % 9 mg. % 3 mg. %	Developed gas gangrene; developed osteomyelitis; finally healed after amputation.
8	R. P.	Severed tendons of wrist	Sutured with silk	Antigas Antitetanus	7 gms.	Initial 90 gr.; 30 gr. q. 4 h.	6 days	8.3 mg. %	Healing per primum. Excellent function.
9	J. D.	Avulsion of calf of leg	Cleansed and debrided	Antigas Antitetanus	40 gms.	Initial 80 gr.; 30 gr. q. 4 h.	8 days	16.5 mg. % (30 hours) 11 mg. % (4 days)	Healing well, no infection.

10	H. McR.	Frostbitten foot	Incision and drainage, later amputation	0	40 gms. 25 gms. 25 gms.	Initial 80 gr.; 20 gr. q. 4 h.	9 days	17 mg. % (30 hrs.) 25 mg. % (8 days)	Gas gangrene developed, healing after amputation.
11	A. H.	Crushing laceration of forearm	Incision	0	25 gms. 25 gms.	Initial 80 gr.; 20 gr. q. 4 h.	5 days	11.5 mg. %	Admitted with gas gangrene. Healed well, later grafted.
12	E. P.	Bullet wound of foot	Debrided	Antigas Antitetanus	30 gms.	Initial 90 gr.; 20 gr. q. 4 h.	7 days	8.3 mg. % 14 mg. %	No infection, filled in with granulation tissue.
13	F. F.	Traumatic amputation of lower leg	Reamputation	Antigas Antitetanus	40 gms.	No initial; 15 gr. q. 4 h.	3 days	3.3 mg.% (6 hrs.) 7.6 mg. %	Healing without infection.
14	J. W.	Compound fracture of thumb	Cleansed	Antitetanus	3 gms.	0	0	0	Healing per primum.
15	W. McK.	Penetrating wound of forearm	Cleansed and debrided	Antitetanus	10 gms.	Initial 80 gr.; 15 gr. q. 4 h.	4 days	5.5 mg. %	Healing without infection.
16	F. DiM.	Compound fracture of 3 fingers	Cleansed and debrided	Antitetanus	5 gms.	Initial 90 gr.; 15 gr. q. 4 h.	4 days	5.2 mg. % 6.7 mg. %	Healing per primum.
17	G. S.	Compound fracture and laceration	Debridement and open reduction	Antitetanus	5 gms.	0	0	0	Healing well.
18	J. C.	Deep laceration of thigh	Cleansed and debrided	Antitetanus	12 gms.	0	0	3.7 mg. %	Healing per primum.

* 1 ampule of antitetanus and 1 ampule of antigas sera unless otherwise designated.

GROUP III

Case No. 8: R. P., a 26 year old colored male, while attempting to open a window, was struck by a pane of glass which landed on the volar surface of his left wrist and severed all of the tendons but not the nerves or arteries. The tendons were sutured with black silk and then 7 grams of sterile powdered sulfanilamide were placed in the wound around the tendons. The subcutaneous tissue and skin were sutured loosely with black silk and a cast was applied. The patient was given routine antigas and antitetanus sera, and put on sulfanilamide with an initial dose of 90 grains and 30 grains every four hours. A blood sulfanilamide level four days later was 8.3 mg. %. He ran a slight elevation of temperature for seven days and from then on it was normal. The patient was discharged thirteen days after admission. When seen in the dispensary two months after admission there was only a slight weakness of the fourth and fifth fingers. There was no evidence of infection around the laceration at any time.

Case No. 9: J. D., a 45 year old white male, was brought to the accident room in a state of marked shock following an automobile accident in which he sustained a severe laceration involving the entire calf, with avulsion of the insertions of the lower portion of the gastrocnemius muscle. The muscle was hanging freely, having been dissected from the soleus muscle. After shock was combated, the leg was carefully cleansed and a large portion of the gastrocnemius muscle debrided. No tendons or nerves were cut. The good portions of the gastrocnemius were sutured to the soleus muscle and the skin flap replaced. Forty grams of sterile sulfanilamide were packed into the wound and between the muscle layers. Petrolatum gauze and a dry dressing were applied. The skin flap had to be debrided later because of dry gangrene, but the remaining tissue showed no evidence of infection and healed promptly. The bare area was grafted with good results. After returning to the ward the patient was given 80 grains of sulfanilamide as an initial dose, followed by 20 grains every four hours. This was discontinued after one week. Approximately thirty-six hours after admission the blood level was 16.5 mg. %. He was given 900 cc. of blood, as well as routine antigas and antitetanus sera. His leg is now completely healed.

Case No. 10: H. McR., a middle-aged colored male, was admitted dazed and confused, as he had lived in a "hobo jungle" for a week. His left foot and lower leg were swollen and the toes were dark, showing early necrosis. Saline compresses were applied to the foot but on the second day there were signs of gas bacillus infection in the foot. It was immediately incised and drained, and sulfanilamide implanted. The next day a low thigh amputation was performed. The stump was left open and 40 grams of sulfanilamide were packed into the wound. Upon the discovery of the gas in the foot an initial dose of 80 grains of sulfanilamide, followed by 20 grains every four hours, was given. The blood sulfanilamide level after amputation was 17 mg. %; however, more sulfanilamide was packed into the wound. Seven days after the operation the leg looked quite clean, so the edges were pulled together with flamed adhesive. However, on the next day the temperature was 104°F., and gas was found in the wound. The wound was reopened and packed with sulfanilamide. Inadvertently, sulfanilamide was still being given by mouth and a blood level taken on this day showed 25 mg. %. This led to the belief that the local application of sulfanilamide is somewhat more efficacious than a high blood level, as the temperature came down promptly after the local application. The wound cleared rapidly and filled in with granulation tissue. Except for an elevation of the nonprotein nitrogen, his progress was quite satisfactory.

Case No. 11: A. H., a 22 year old colored male, had a crushing laceration of the left forearm which was sutured at another hospital. In twenty-four hours it was obviously infected and he was sent to the Baltimore City Hospitals, where it was noted that a few bubbles of gas were escaping from an infected wound. The patient was given sulfanilamide by mouth, and sulfanilamide in tragacanth was packed into the wound after the sutures had been removed. Smears showed B. welchii on the following day. Approximately forty-eight hours after admission, the arm was quite swollen, the tissues were much more tense, and the crepitant area was larger. The patient was anesthetized and the laceration extended up to the olecranon and through the fascia, and the muscle exposed. Considerable hematoma was found beneath the fascia and the tissues were under so much tension that the edges separated about 6 to 8 cms. Twenty-five grams of sulfanilamide were packed into the wound and a dry dressing applied. The next day the arm looked much better; however, an additional amount of 25 grams of sulfanilamide was packed into the wound. The blood sulfanilamide level at this time was 11.5 mg. % and the patient was receiving 20 grains every four hours after an initial dose of 80 grains. Six days after admission the tissues were relaxed and there was no evidence of gas. The wound rapidly filled in with granulation tissue and only a few small pinch grafts were necessary. The patient had no loss of function and left the hospital after thirty-five days. No antigas serum was given.

Case No. 12: E. P., an 18 year old white male, was admitted to the hospital after accidentally discharging a 12 gauge shotgun through the right foot. The roentgenogram revealed fractures of the third, fourth, and fifth metatarsal bones. He was given routine antigas and antitetanus sera. The foot was cleansed and debrided, and 30 grams of sulfanilamide were packed into the wound. A large hole was left in the foot. The patient was given 80 grains of sulfanilamide immediately and 20 grains every four hours thereafter. The next morning the blood level was 8.3 mg. %, and three days later it rose to 14 mg. %. The wound granulated in slowly and at no time was there any evidence of infection. The foot is now healed and the patient has no loss of function.

In reviewing these cases it might be stated that the first one represented a relatively simple problem. The latter cases were dirty lacerated wounds. The blood level of 16.5 mg. % thirty-six hours after entry in the third case is of interest. It was impossible to close this wound entirely, but the marked absorption shows that the primary closure is not a prerequisite to the desired local and general effects of the drug.

The authors believe that these three groups of cases represent the evolution of treatment and prophylaxis of gas gangrene in the Baltimore City Hospitals. There are, obviously, too few cases from which to draw many conclusions. Nevertheless, it is significant that in the patients who have had adequate dosage of sulfanilamide, checked with frequent blood levels, there have been no deaths.

An abbreviated summary of the above twelve cases is included. The first four represent those that did not receive sulfanilamide therapy; all died. Cases Nos. 5, 6, and 7 were treated with sulfanilamide by mouth, in addition to recognized surgical treatment. All cases in group II recovered but had a long hospitalization. Cases Nos. 8, 9, 10, and 11 are described above, and with Cases Nos. 12 through 18 represent those treated by implanting sulfanilamide into the wound. Cases Nos. 10 and 11 had gas gangrene. The remaining cases represent those that could easily have developed not only a mild infection but also gas gangrene. In the third group of cases all healed by primary intention except Case No. 10, which filled in with granulation tissue after amputation. All patients in group III recovered.

COMMENT

As a result of the experience gained with these relatively few cases it is believed that certain facts are evident. Implantation of sulfanilamide into a dirty laceration is a more useful prophylaxis than simple cleansing and debridement. Sulfanilamide locally implanted is more effective against gas forming bacilli than sulfanilamide taken by mouth. Furthermore, a high blood level obtained by oral administration of sulfanilamide does not insure the patient against gas gangrene. Prophylactic injection of antitoxin is likewise no insurance against development of gas infection. No severe general effect from implantation of as much as 50 grams of sulfanilamide has been observed, nor has reference to local implantation of sulfanilamide into wounds infected with gas forming bacilli been found.

CONCLUSION

1. Immediate local cleansing and debridement, with implantation of sulfanilamide is the best prophylaxis employed by the authors against gas gangrene.
2. In the presence of clinical and laboratory evidence of gas bacillus infection, the best methods of therapy are:
   a. Careful local debridement with implantation of large amounts of sulfanilamide.
   b. Administration of large doses of sulfanilamide by mouth.
   c. Supportive blood transfusions.

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CHEMISTRY OF THE SEX HORMONES AND RELATED SUBSTANCES*†

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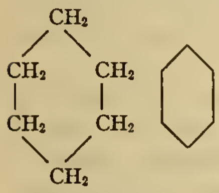
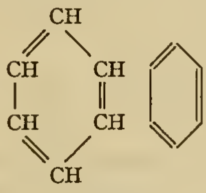
The unraveling of the complicated problem of the nature of sterols, bile acids, and related substances is one of the outstanding achievements of modern organic chemistry. The determination of the structures was an extremely difficult problem, but these compounds are of such importance in physiological processes that investigations initiated over a century ago were pursued with fearless zeal. The structural formulas which were assigned to these substances show that the problem was inherently difficult, for the compounds are very complex and not easily purified. The yields which are obtained from reactions of these materials are usually poor. It was necessary to invent a whole new science, that of micro-analysis and the development of microtechnic, in order to solve the problem.

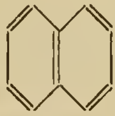
Sterols, bile acids, sex hormones, adrenal substances, toad poisons, and heart poisons occurring in plants are all related to the same polycyclic nucleus, namely, to the cyclopentanoperhydrophenanthrene nucleus.



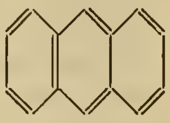
Cyclohexane



Benzene



Naphthalene



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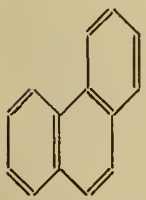
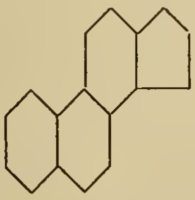
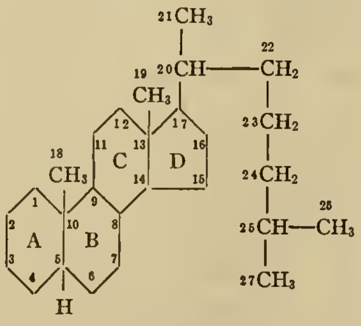


Phenanthrene



Cyclopentanoperhydrophenanthrene



Cholestane

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* From the Department of Pharmacology, School of Medicine, University of Maryland.

† Presented before the Journal Club of the University of Maryland, December 4, 1940, as a review of the chemistry of the sex hormones and related substances.

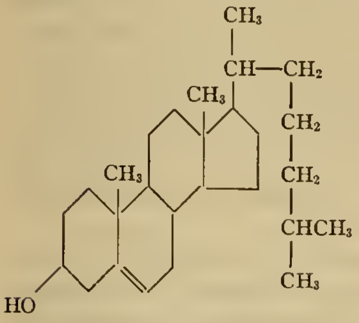
The formulas shown above illustrate what is meant by this term. When six carbon atoms, each holding two hydrogens, are arranged in a ring, the compound is called cyclohexane. It can be represented by either of the two methods shown. Benzene has three double bonds in the ring and these double bonds are indicated by drawing a line inside the hexagon for each double bond. Naphthalene has two benzene rings fused together, while anthracene has three fused benzene rings in a straight line. If one of these three rings is placed at an angle, phenanthrene results. A perhydrophenanthrene has no double bonds. The prefix, cyclopentano, indicates that there is a five-membered ring attached. Thus, cyclopentanoperhydrophenanthrene is a completely saturated phenanthrene with a five-membered ring. Cholestane is the parent hydrocarbon of cholesterol. The carbons are numbered to facilitate the naming of derivatives of cholestane. All similar compounds are numbered in the same way, but the numbers are not usually shown. The rings are designated by letters.

The formula of cholestane is even more complicated than would appear at first glance. Whenever a carbon atom holds four different groups, it is called asymmetric. The groups can be considered as being located at the corners of a regular tetrahedron with the asymmetric carbon in the center. These groups can be arranged in two different ways, so that the two arrangements are not superimposable, but are mirror images. Two molecules that differ in this way are called stereoisomers. An analogous difference exists between the right and left hands.

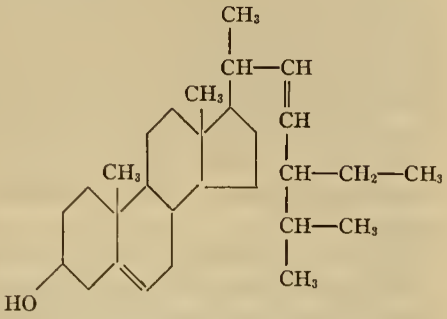
When a molecule has many asymmetric carbon atoms, the number of possible isomers increases very rapidly. Thus, in cholestane, carbons Nos. 5, 8, 9, 10, 13, 14, 17, and 20 are asymmetric and there is a possibility of 256 stereoisomers. If there is an hydroxyl at carbon No. 3, as there frequently is in sterols, there are 512 possible isomers.

Carbons Nos. 5 and 10 are common to two rings. Each is attached to three ring carbons. If the rings are assumed to be in the plane of the paper, the fourth group attached to each of these carbons can be in a plane either above or below the plane of the rings. The groups attached to carbons Nos. 5 and 10 can be either both on the same side of the molecule, or one can be above the rings and the other below the rings. If a group is above the rest of the molecule, it is represented as being attached by a solid line. If the group is below the rest of the molecule, a dotted line is used. Carbons Nos. 8 and 9 and carbons Nos. 13 and 14 are two similar pairs. The groups attached to carbons Nos. 13 and 14 are always on opposite sides of the rest of the molecule. The groups on carbons Nos. 8 and 9 are on opposite sides, except in the cortical hormones where they may be on the same side of the molecule.

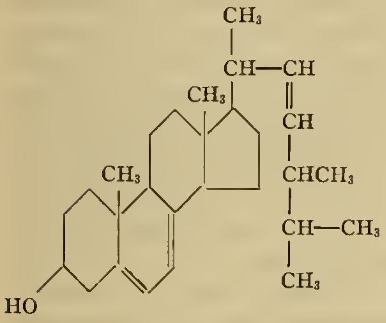
These differences are not trivial, for profound differences in physiological properties occur as a result of such changes.



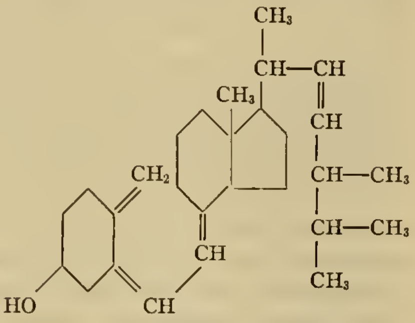
Cholesterol



Stigmasterol (a Phytosterol)



Ergosterol



Vitamin D_2 or Calciferol

These formulas give a few examples of sterols. Cholesterol and stigmasterol differ only in the side chains. Ergosterol has an additional double bond and a different side chain. Vitamin D_2 is formed from ergosterol, which has lost the methyl group at carbon No. 10, gained a double bond and opened ring B to yield the vitamin.

Calciferol is formed by irradiation of ergosterol. Cholesterol can be irradiated to a substance which is half as active as calciferol. This fact opens the possibility that vitamin D may not be one compound but may vary with the source, since a number of antirachitic substances are known.

Biological experiments have established that all sexual activity proceeds under the influence of certain chemical substances. These are the sex hormones which have a close chemical relation to the sterols. They can be classified into a number of types. There are the female sex hormones, which are divided into the follicular hormones and the hormones of the corpus luteum. There are the male hormones of which there is only one type. Finally, there are the gonadotropic hormones which are nonspecific as to sex.

Sex hormones appear to be formed in the testes or in the ovaries under the stimulation of gonadotropic hormones secreted by the anterior lobe of the pituitary. Those hormones control the growth and physiological functioning of the reproductive organs and, according to their nature, promote the development of either the male or female secondary sex characteristics.

The male hormones control development of the genital tract and the accessory male organs, and they influence the longevity and motility of the sperm.

The female hormones control the uterine cycle. In humans this consists of the periodic preparation of the uterus for pregnancy. The first phase occurs under the influence of the follicular hormone which is called estrin. This hormone is produced in the ovaries and passes through the blood stream to the uterus. It stimulates the growth or proliferation of a functional bed or mucosa in the uterus. The second phase of the cycle is the secretory phase and occurs under the influence of the hormone of the corpus luteum, called progestin. It prepares the functional bed for the implantation of the fertilized ovum. If there is no fertilization leading to pregnancy, the mucosal bed degenerates and returns to the unproliferated or resting state.

The gonadotropic hormone is secreted by the anterior lobe of the pituitary and passes into the blood stream to the testes or ovaries, where it stimulates the production of the male or female sex hormones.

Removal of the pituitary gland arrests all sexual activity. Its removal from female animals before puberty leads to infantilism. If the operation is carried out at a later period, cessation of the sex cycle occurs and the ovaries become atrophic. The implantation of pituitary tissue to such female animals restores the normal cyclic changes. If the gland is removed from male animals, the reproductive organs degenerate. Implantation of the pituitary gland will regenerate these organs. Such implantations have no effect on castrated animals.

These experiments show the relationship between the anterior lobe of the pituitary and the gonads. They establish the role of the pituitary gland in the control of the sexual processes. By using cell-free extracts of the pituitary it has been shown that the control is hormonal. However, the hormones which are involved have not been fully characterized as yet.

In a similar manner the hormonal character of the other sexually active compounds can be demonstrated. The administration of estrin will produce estrus in ovariectomized animals. Progestin will produce progestational proliferation of the mucosa in adult female rabbits which have been castrated at the proper stage of follicle ripening as determined by mating. These changes are recognizable by histological examination. Infantile female rabbits will produce a similar endometrium after administration of this hormone. The male hormones will cause the comb and wattles of a capon to resume growth, and the seminal vesicles of castrated male rodents develop on administration of such hormones. These changes are utilized to assay the activity of extractions and the potency of pure compounds.

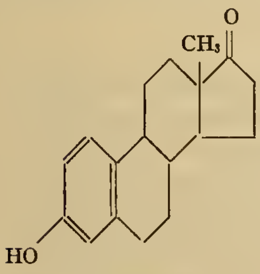
The terms, estrin and progestin, are general terms used for any compound which will produce the specific hormonal activities mentioned previously.

Estrone is an estrin which is obtained from the urine of pregnant women in a concentration of 1 mg./l. The urine of pregnant mares contains about 10 mg./l. It has been calculated that a mare will produce during pregnancy as much estrone as can be obtained from 1500 patients at a maternity clinic. Surprisingly enough, the urine of stallions contains almost twice as much estrone as that of pregnant mares, and the testes of a stallion contain 300 times as much estrone as the ovaries of a sexually mature mare. Estrins have also been isolated from the vegetable kingdom.

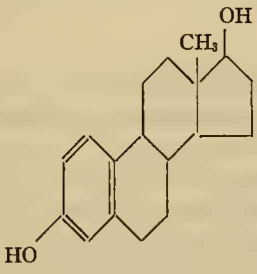
Progesterone occurs in the placenta. The corpus luteum from sow ovaries is used as the starting material for obtaining the hormone. Progesterone is a highly specific substance. It is the only known compound which gives the characteristic test in bio-assays. Alterations of this molecule produce inactive compounds.

Large quantities of estrone are excreted by pregnant women because the hormone is not used, since the uterine cycle is suspended during pregnancy. Nonpregnant, mature females do not excrete estrone which is used to control the uterine cycle. Pregnancy urine does not contain any progesterone because it is used to control the development of pregnancy. Large quantities of reduction products of progesterone are eliminated during pregnancy. It is not known whether or not progesterone occurs in nonpregnancy urine.

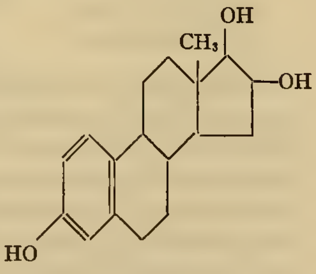
Testosterone is probably the only hormone of the testes. The excreted substance, androsterone, is less active than the hormone. It is either a companion substance or a degradation product of the true hormone.



Estrone

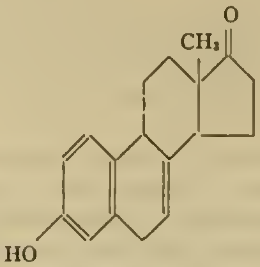


Estradiol

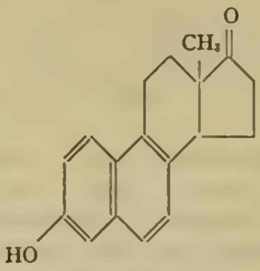


Estriol

Estradiol is more active than estrone. It was made from estrone by reduction before it was isolated from natural sources. Estriol can be converted to estrone by potassium acid sulfate fusion.



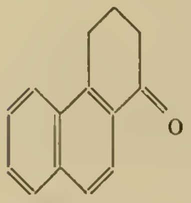
Equilin



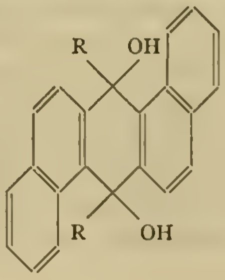
Equilenin

These two substances are active compounds which have been isolated from mares' urine.

The benzoate of estrone has more protracted action than estrone. The phenolic benzoate of estradiol is not only more active than estrone, but it has a more protracted action. Likewise, the diols from equilin and equilenin are more active than the ketones. The oxidation product in which ring D has been opened is seven or eight times as active as estrone. These more active compounds bring up the possibility that estrone is not the true hormone, but that it is a degradation product or companion substance.

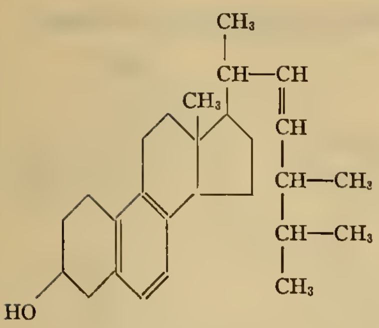


1-keto-1,2,3,4-tetra-
hydrophenanthrene

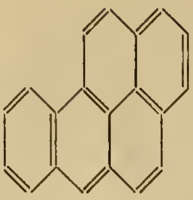


R	Active Dose
Ethyl	1 mg.
n-Propyl	0.025 mg.
n-Butyl	0.1 mg.
n-Amyl	Inactive

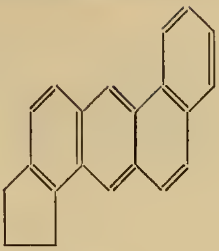
1-keto-1,2,3,4-tetrahydrophenanthrene has slight estrogenic activity. The activity of the dibenzanthraquinone derivative shown next to it depends on the character of the R groups. A comparison of the activities with various R groups can be made from the adjacent table. These compounds do not occur naturally but are products of the laboratory. Most of the sterols are inactive but highly unsaturated ones are active. Ergosterol, calciferol and neoergosterol will produce estrus. Some hydrocarbons are active, but these are also carcinogenic.



Neoergesterol



1,2-Benzpyrene



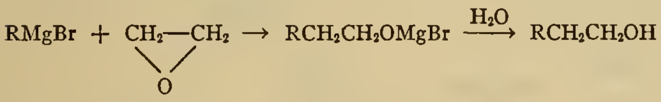
5,6-Cyclopenteno-
benzanthracene

The hydrocarbons are active in 100 mg. doses.

It is possible to synthesize equilenin in the laboratory from starting materials which have never been associated with living matter. Further, it is possible to convert equilenin to estrone which constitutes a total synthesis of a hormone.

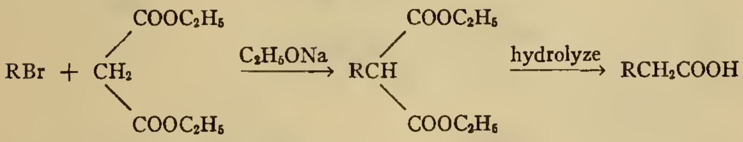
The following reactions are frequently used in such syntheses:

$$RBr + Mg \xrightarrow{\text{ether}} RMgBr$$



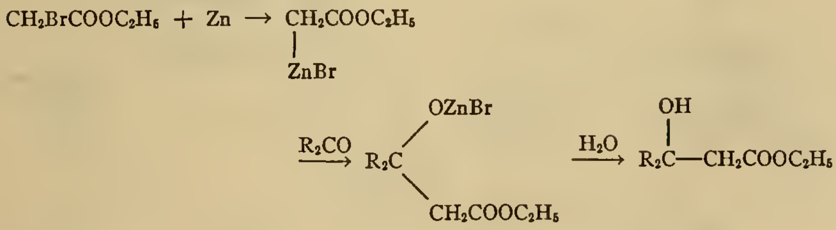
$$RMgBr + \underset{\diagdown\, O \,\diagup}{CH_2{-}CH_2} \rightarrow RCH_2CH_2OMgBr \xrightarrow{H_2O} RCH_2CH_2OH$$

$$RMgBr + RCOCl \rightarrow RCOR$$



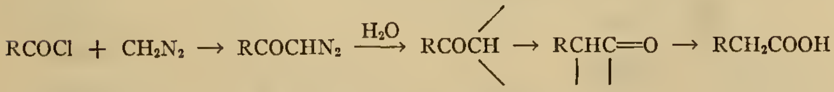
$$RBr + CH_2\begin{matrix}\diagup COOC_2H_5\\ \diagdown COOC_2H_5\end{matrix} \xrightarrow{C_2H_5ONa} RCH\begin{matrix}\diagup COOC_2H_5\\ \diagdown COOC_2H_5\end{matrix} \xrightarrow{\text{hydrolyze}} RCH_2COOH$$

$$RCOOH + PCl_5 \rightarrow RCOCl$$

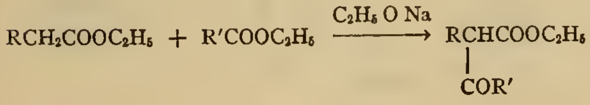


$$CH_2BrCOOC_2H_5 + Zn \rightarrow \underset{\underset{ZnBr}{|}}{CH_2COOC_2H_5}$$

$$\xrightarrow{R_2CO} R_2C\begin{matrix}\diagup OZnBr\\ \diagdown CH_2COOC_2H_5\end{matrix} \xrightarrow{H_2O} R_2\overset{\overset{OH}{|}}{C}{-}CH_2COOC_2H_5$$

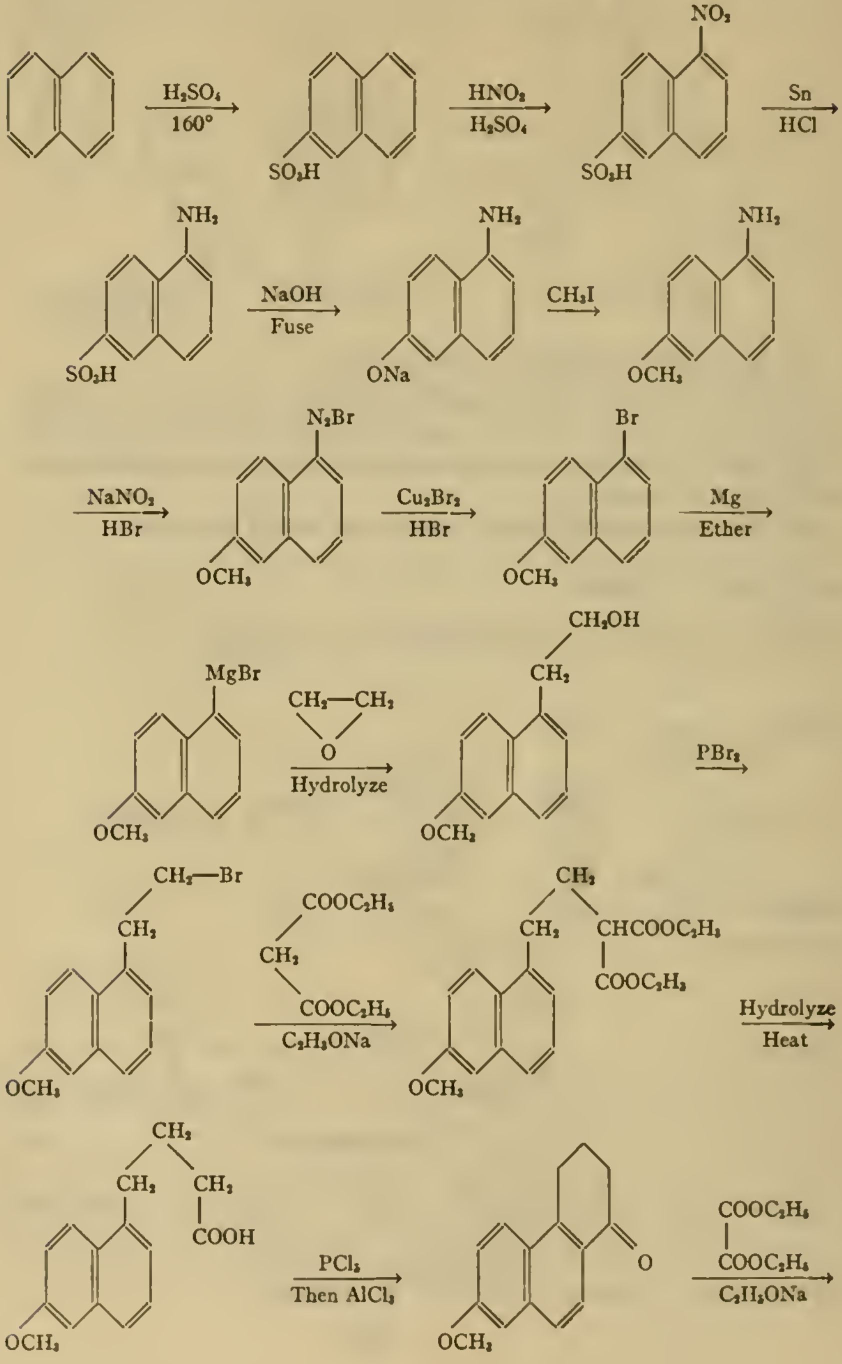


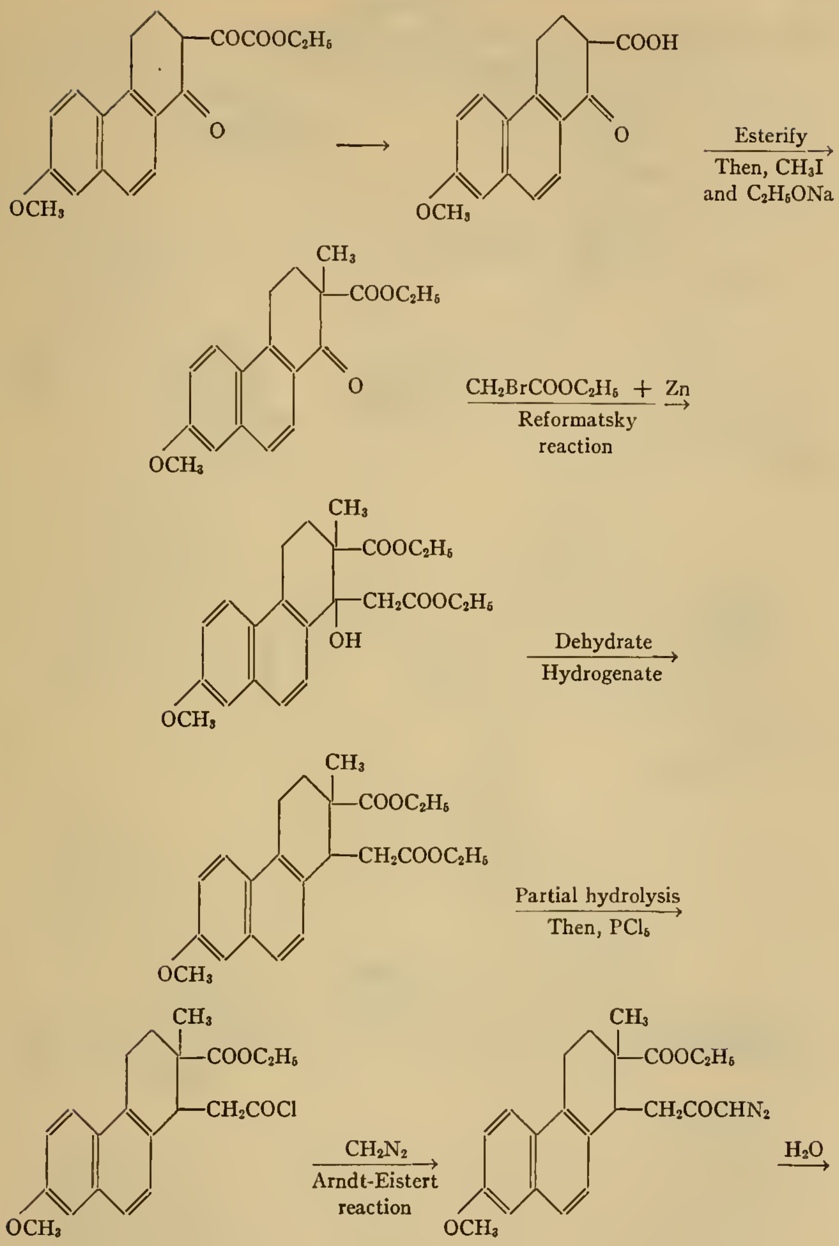
$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 \xrightarrow{H_2O} RCOCH\begin{matrix}\diagup\\ \diagdown\end{matrix} \rightarrow R\underset{|}{C}H\underset{|}{C}{=}O \rightarrow RCH_2COOH$$

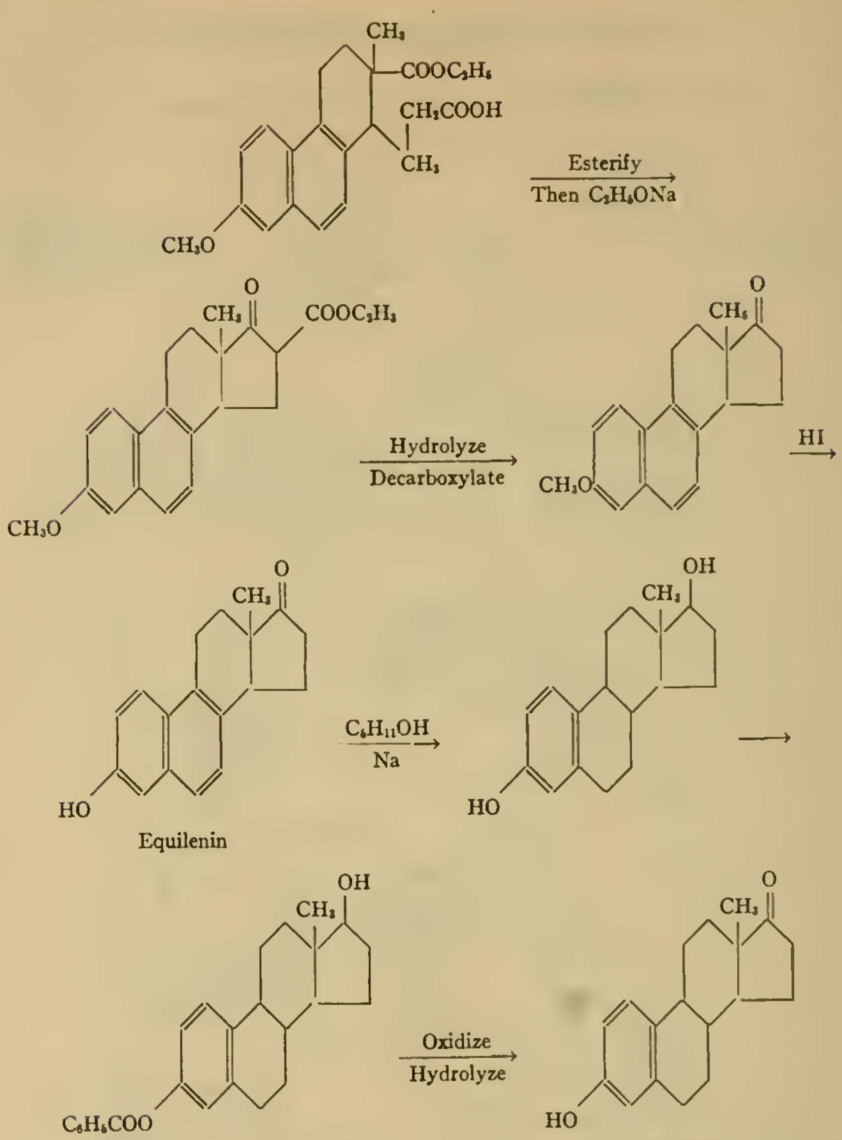


$$RCH_2COOC_2H_5 + R'COOC_2H_5 \xrightarrow{C_2H_5\,O\,Na} R\underset{\underset{COR'}{|}}{C}HCOOC_2H_5$$

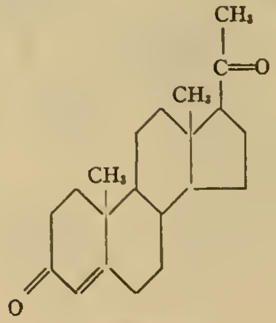
The following reactions outline the synthesis of equilenin and estrone:




—COCOOC₂H₅
O
OCH₃
—COOH
O
OCH₃
Esterify
Then, CH₃I
and C₂H₅ONa
CH₃
—COOC₂H₅
O
OCH₃
CH₂BrCOOC₂H₅ + Zn
Reformatsky
reaction
CH₃
—COOC₂H₅
—CH₂COOC₂H₅
OH
OCH₃
Dehydrate
Hydrogenate
CH₃
—COOC₂H₅
—CH₂COOC₂H₅
OCH₃
Partial hydrolysis
Then, PCl₅
CH₃
—COOC₂H₅
—CH₂COCl
OCH₃
CH₂N₂
Arndt-Eistert
reaction
CH₃
—COOC₂H₅
—CH₂COCHN₂
OCH₃
H₂O

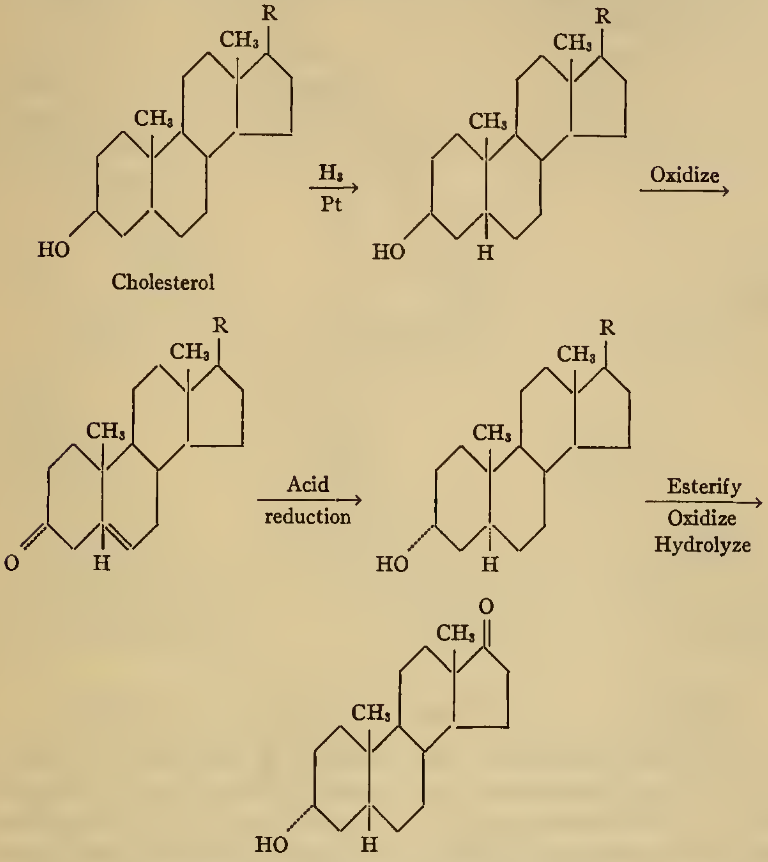


Estrone



Progesterone

Progesterone can be made from stigmasterol or from pregnanediol. Androsterone has been synthesized from cholesterol.



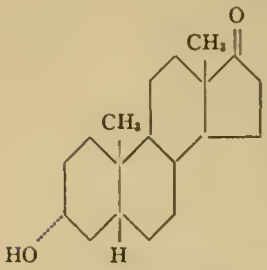
Cholesterol

Androsterone or 3-Epihydroxyetioallocholanone-17

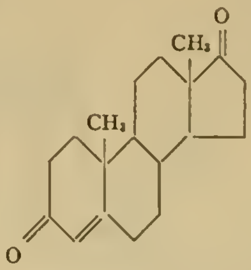
The compounds listed below, except the last two, have hormonal activity. Their potencies are compared by giving the doses equivalent to one capon unit.

	γ/capon unit
Androsterone	150–200
Androsterone acetate	150–170
Androsterone oxime	1,000
Androstanediol-3,17	45–50
Androstanediol-3,17-diacetate	60–70
Androstanedione-3,17	300
Androstanone-17	2,000–3,000
Dehydroisoandrosterone	600
17-Methylandrostanediol-3,17	75

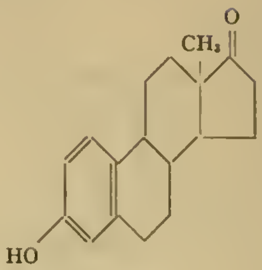
	γ/capon unit
3-Hydroxyetioallocholanone-17 (or isoandrosterone)	1,500
3-Hydroxyetiocholanone-17	3,000
3-Epihydroxyetiocholanone-17	3,000



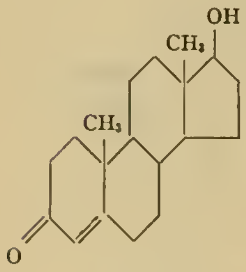
Androsterone



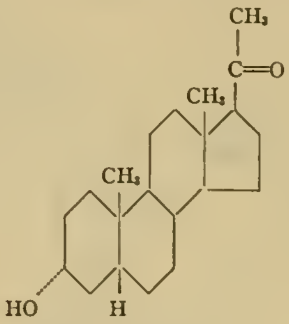
Androstenedione-3,17



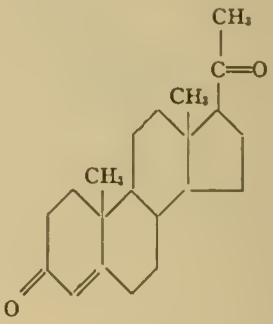
Estrone



Testosterone



Epiallopregnanol-3-one-20



Progesterone

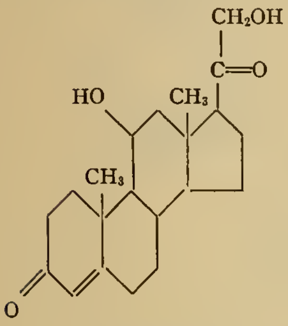
The remarkable similarity of the structures of these compounds should be noted. Androsterone has male hormonal activity but no estrogenic activity. Androstenedione-3,17 is two-thirds as active as androsterone and it also has estrogenic activity. It is intermediate in structure between androsterone and estrone. Androsterone differs from estrone only by three double bonds and a methyl group. Testosterone is very similar to androsterone. Epiallopregnanol-3-one-20 is the hormone present in pregnancy urine, and it is responsible for the male hormonal activity of pregnancy urine. Finally, there is progesterone for purposes of comparison.

Closely related in chemical structure to these compounds are certain cortical substances. It has been shown by experiment that adrenalectomized dogs cannot live unless extracts of the cortex are administered. The animals can make up the deficit of adrenalin but not the hormones of the cortex. Regular injections of the hormones will keep such dogs alive and capable of reproduction. The dogs die if the injections are discontinued. The bio-assay of these preparations is based on the quantity necessary to keep these dogs normal.

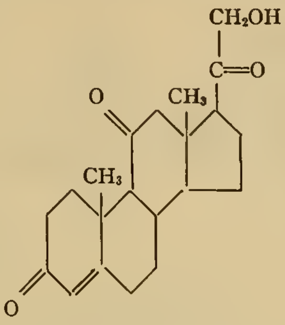
Cortin is used clinically in Addison's disease, when the cortex is destroyed by tuberculosis or atrophy.

One kg. of cortex glands from cattle yields 60 mg. of dry substance containing 1000 to 2000 dog units. A dog unit is the minimum daily dose needed to keep an adrenalectomized dog normal for seven to ten days. There must be no loss of weight, no vomiting, and no rise of nonprotein nitrogen in the blood.

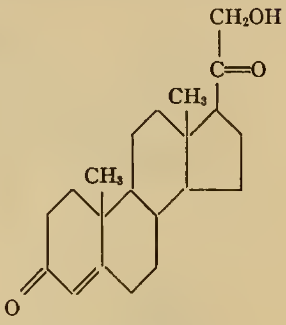
The following active compounds have been isolated from extracts of the adrenal cortex:



Corticosterone

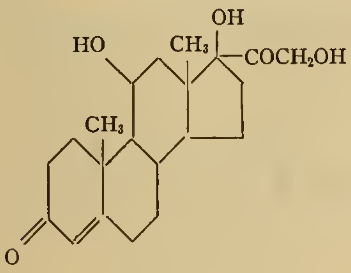


Dehydrocorticosterone

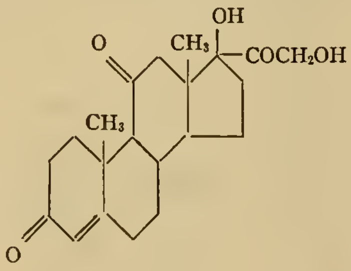


Desoxycorticosterone

The first two are equally active, but the next one is four times as active. The next compound below has some activity, and the last one is fairly active.

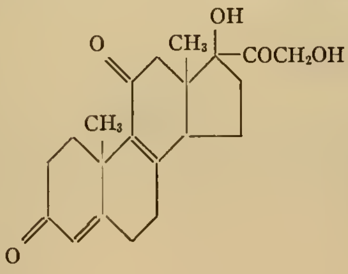


Substance M



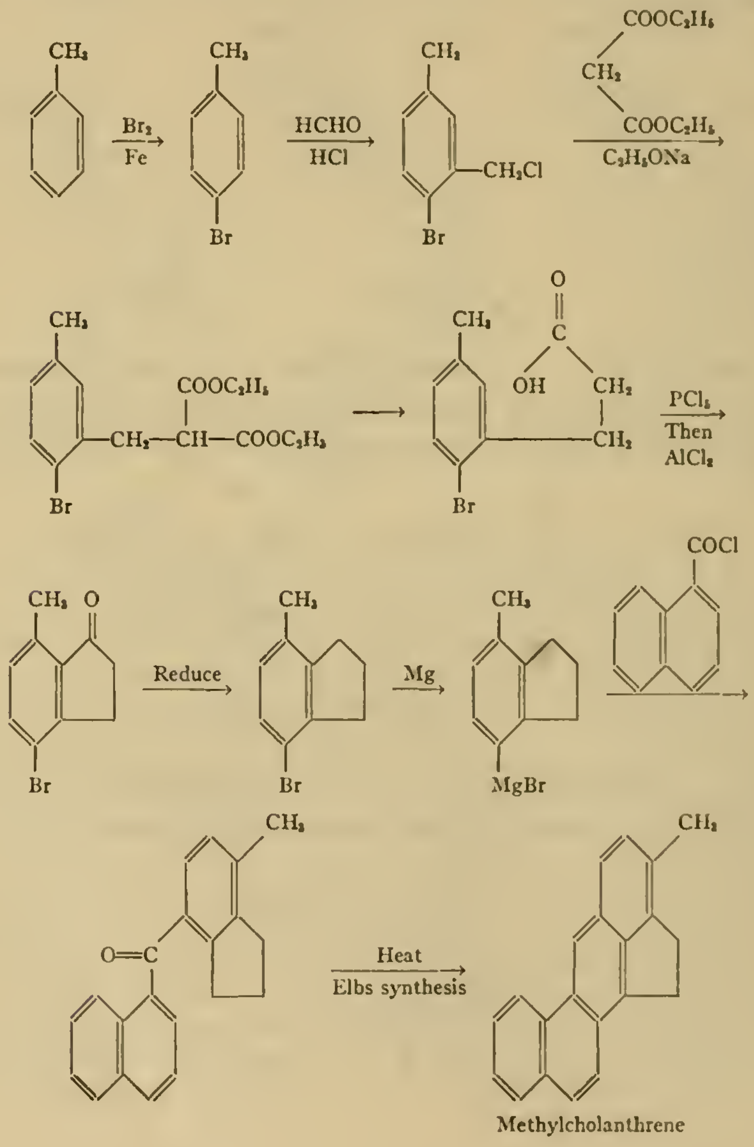
Substance Fa

Many other compounds have been isolated but they have no activity.

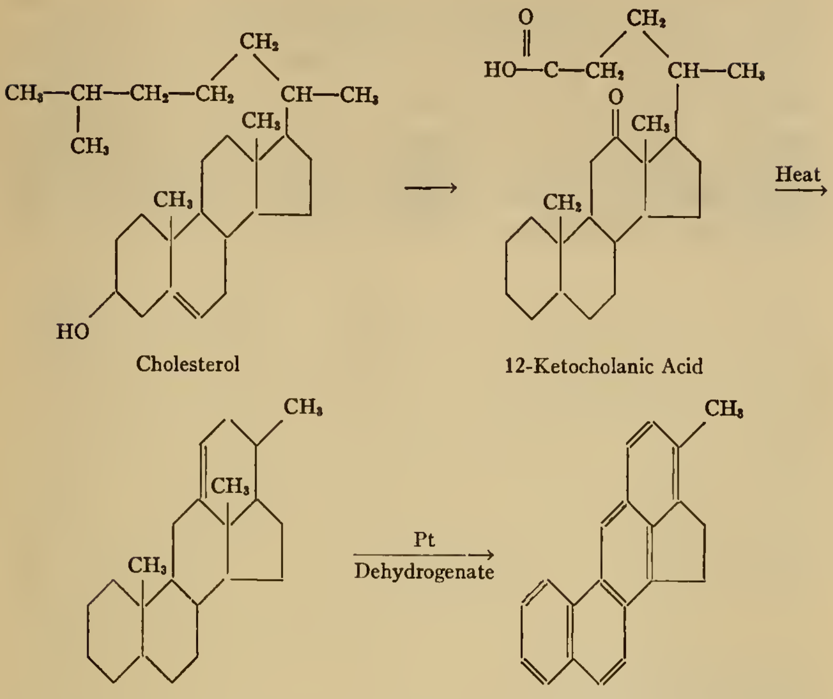


Pregnadiene-4,8-diol-17,21-trione-3,11,20 is considered by some experimenters to be the precursor of all cortical substances. This compound can also account for the sex hormones. It is a hypothetical substance because it has never been isolated.

Less closely related to the substances which have been discussed are the carcinogenic hydrocarbons. Certain polycyclic hydrocarbons will produce cancer when they are injected into animals or painted on the skin. Methylcholanthrene is one of the most active. It has been synthesized as follows:



This substance can be synthesized from cholesterol:

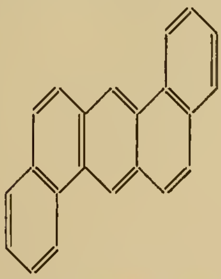


Cholesterol

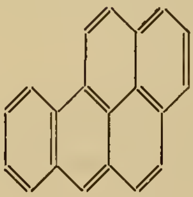
12-Ketocholanic Acid

Methylcholanthrene

Other cancer-producing hydrocarbons are:



1,2,5,6-Dibenzanthracene



1,2-Benzpyrine

1,2-Benzanthracene is inactive, but substitutions in the 5 and 6 positions yield cancer-producing hydrocarbons. Substitutions in other positions do not yield active compounds.

The ubiquitous nature of the phenanthrene nucleus should be noted. It is present in cholesterol, which is distributed through the entire body. It controls sexual activity for the same nucleus is present in the sex hormones, both male and female. Further, it is present in certain cortical substances necessary for life. A slight modification of the molecule results in a cancer-producing substance. Man is now master of his destiny. He has modified these molecules to produce more active hormones. These hormones, which are so closely related chemically, produce divergent effects physiologically. Some of the differences in structure consist only of a different spacial arrangement of the same groups. Is it too much to expect that some modification of the same compounds which produce cancer will result in compounds which will prevent and cure cancer?

SCALP FORCEPS IN OBSTETRICS*†

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BALTIMORE, MD.

In the practice of obstetrics, conditions occasionally arise which appear to render advisable a more rapid delivery than would occur normally. There are a number of methods available to produce this result, some radical and some conservative, but none applicable to all cases, although each has certain points in its favor.

The abdominal route for delivery as a routine procedure is entirely too radical and carries with it those inherent dangers which make the conscientious obstetrician look for a simpler and, at the same time, a safer method. The Braxton Hicks bipolar version, while comparatively safe for the mother, automatically includes a death penalty for the child. The use of hydrostatic dilators or, as it is usually called, bagging, frequently introduces infection and dislodges the presenting part, thereby increasing the possibility of prolapse of the cord or malpresentation. Furthermore, this step does not result in delivery as some operative procedure usually is necessary. The Spanish windlass probably should be reserved for a few selected cases, especially those in which hemorrhage is an outstanding feature.

The majority of all presentations are cephalic and, as a rule, when the indication for interference arises the problem is one of an insufficiently dilated cervix, a presenting part which is not accurately applied to it, or insufficient uterine contractions. Frequently, more than one of these conditions are present. All of the suggested methods of treatment other than cesarean section have as their object continued pressure against the cervix. This causes uterine irritation, that is, an increase in the frequency and force of contraction and cervical dilatation.

The admitted disadvantages of the bipolar version and bagging should be borne in mind and another method of producing this result should receive careful consideration. If it seems safe enough, it should be tried. For example, when the method of Willett, the application of a forceps to the baby's scalp, was advanced some years ago, it was carefully studied and the method given a trial.

Willett first reported his experience with the scalp forceps in 1925 (12). While he appeared quite enthusiastic, he did not follow up his original report and the attention of the medical public was not attracted to any extent. There was a scarcity of references to this method in the literature

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† Received for publication November 18, 1940.

until 1932. After this only sporadic articles appeared, but recently these have increased.

The author's own experience has been quite satisfactory. He feels that the method deserves a great deal more attention and a much wider use than it has received. In this article are reported only a few of the cases in which the scalp forceps was used. The selection was made for the sake of brevity and to demonstrate the indications for this instrument. The results are characteristic for the entire series.

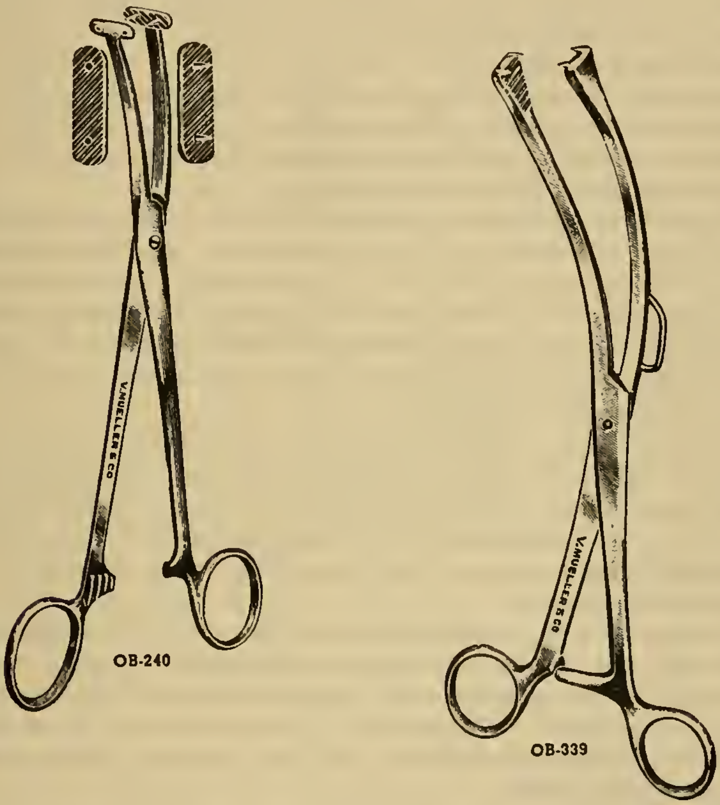
There have been a number of instruments devised for the purpose of scalp traction. Willett originally used a Mantel's forceps which was later modified to the one which now bears his name. DeLee (2) suggested a modification of the latter but believes that an ordinary vulsellum or myoma forceps suffices. Gauss (3) designed a new forceps entirely. All of these forceps involve the same principle and apparently do not possess outstanding superiority over one another. In this series a variety of these instruments was employed, largely as a matter of experimentation.

The forceps must have a fairly long handle and a bite, generally T-shaped, of sufficient width and firmness to insure a secure grasp. Serrated teeth may or may not be present, but a bite augmented by the addition of a pair of pronglike formations is an advantage. The latter is the basic design of both the Willett and Gauss instruments.

The technic is simple and may be used in primipara or multipara. When the membranes are ruptured (with the instrument itself, if so desired) and the cervix is sufficiently dilated to allow for the introduction of the clamp, the forceps is inserted under the guidance of the finger and attached to the scalp of the fetus as near the occiput as possible. If the head is floating it may be necessary to exert pressure upon the fundus or lower uterine segment to manipulate the head into a position favorable for grasping. After it has been made secure there is attached to the clamp a tape or length of gauze which runs over a pulley at the edge of the bed and to which is fastened, in turn, a one-fourth to one-half pound weight that is held in suspension. This weight should not be greater than specified or heavy enough to cause damage to the maternal soft parts, such as laceration of the cervix, but sufficient to hold the head firmly against the lower uterine segment and irritate the uterus to increased activity. Although some writers claim that the instrument should be removed after six hours or after the head is engaged in the pelvis, it has been the author's experience that it may remain safely in place until the second stage of labor is completed, or a maximum of twelve hours.

After the real value of the Willett clamp was established satisfactorily in certain cases of placenta previa (the marginal type with partial dilatation of the cervix) and in premature separation of the low implanted placenta, the author began to widen the indications for its use and now employs it rather frequently for the following:

1. To stimulate labor in uterine inertia and to hasten its termination in the presence of toxemia and infection.
2. For traction on the dead fetus to empty the uterus when this is desirable.
3. To prevent prolapse of a fetal part or cord in cases of floating head with ruptured membranes.



Courtesy V. Mueller & Co., Chicago

FIG. 1

4. To correct malposition of the head and to maintain the new position.
5. As an adjunct to amniorhexis for the induction of labor when there arises an obstetrical complication.

It should be remembered that only a slight amount of cervical dilatation is required for the application of the clamp and that it may be used quite early in labor.

When used for the induction of labor it is found that the latent period is considerably shortened, thus reducing the likelihood of infection and preventing the rapid escape of amniotic fluid. Should labor be too tempestuous, the clamp may be removed at any time and without any preparation of the patient.

It has been found that traction on the fetal scalp stimulates labor pains and there are many instances, especially in multipara, in which some stimulation is necessary to further the progress of labor. This method removes, in many cases, the necessity for the administration of oxytocic drugs, some of which have the tendency to further tire the uterus, whereas direct gentle mechanical stimulation does not force the uterus beyond its normal contractile capacity. In the presence of the toxemias and infection, where it is considered that the duration of labor has a vital influence upon the ultimate outcome of these conditions and upon both the mother and the fetus, this method should be employed in preference to the more dangerous high or midforceps extraction.

Frequently cases are seen of a prolapsed fetal part or cord before complete dilatation of the cervical os. It is suggested that the Willett clamp be applied after replacement when such a danger exists. The author is not unmindful, however, that the process of applying the clamp exposes one to this type of accident and that extreme caution must be observed. Again, an insecurely attached clamp is liable to tear away and this may be followed by a prolapsed fetal part or cord.

In cases of known fetal death, craniotomy and forceful extraction of the child, especially in the presence of infection, is certainly less desirable than scalp forceps traction with the relatively small amount of manipulation involved. The latter method does not necessitate as much initial cervical dilatation, and does not injure the birth canal or subject the patient to as much risk of infection.

Unusual varieties of vertex presentation other than the occiput type sometimes occur. Such cases may be corrected properly by vaginal manipulation and the attachment of a scalp clamp to a portion of the fetal scalp at or near the occiput. The traction will insure permanency to the newly converted position and thus provide relief from possible dystocia caused by positional disproportion.

Scalp lacerations are a complication of this method. The majority of authors have a tendency either to minimize or ignore them entirely. The author does not feel that they are of sufficient importance to contraindicate the use of the Willett forceps, but believes that they result from poor application of the instrument or the use of too heavy a traction weight. Recently F. J. Browne (1) reported two cases of B. welchii infection of the mother and baby following scalp lacerations, and because of these concluded that the method should have no place in the treatment of placenta previa.

He admits, however, that fetal mortality in placenta previa is definitely lower with this method than that for the average mortality, including all modes of treatment.

The author's series of twenty-three cases is small and of a preliminary nature; however, an effort is being made to employ this method whenever it is indicated. This is done in order to reveal, if possible, more conclusive evidence in its favor and because the author is thoroughly convinced of its value.

There were twelve cases of premature separation of a low implanted placenta, two of vaginal bleeding of undetermined origin, four of uterine inertia, two of induction of labor, one of placenta previa marginalis, one of occiput posterior in a second twin, and one of premature separation of a normally implanted placenta. The cases of uterine inertia were complicated by other factors, three of which made the rapidity of labor desirable. These were two cases of chronic nephritis, one moderately severe and the other complicated by convulsions, and a rheumatic cardiovascular disease. The fourth case of inertia was complicated by a transverse arrest of the vertex which caused prolonged labor.

The average duration of the latent period between the application of the clamp and the onset of labor in thirteen cases was one hour, one-and-one-half minutes. The average duration of labor was eight hours, one minute. Of those already in labor, the average labor before application of the clamp was twenty-one hours, forty-five minutes, while the average following application of the scalp forceps was nine hours, seven minutes. Although the small number of cases is inconclusive, it would seem that the scalp clamp inaugurates labor quite promptly and also hastens it.

There were six stillbirths, three of which were intra-uterine deaths before the clamp was applied. One was a premature separation of the normally implanted placenta, another was a premature separation of the low implanted placenta, and the third a severe chronic nephritis. The fourth stillbirth resulted from a labor of fifty hours, forty-two minutes. It seems likely that a possible reversal of the results might have been obtained had the clamp been applied earlier. The fifth was a hydrocephalic fetus delivered by low forceps and was found to be premature, the gestation period having been terminated at the end of thirty-six weeks. The sixth was a premature fetus of thirty-four weeks in a case of placenta previa partialis, in which induction of labor was carried out with the clamp.

The temperatures of two patients exceeded the morbidity level of 100.4°F. on two successive days, and in one patient reached 100.4°F. on one day. The latter had a total duration of labor, with membranes ruptured, of three hours, forty-three minutes. There were fifteen spontaneous deliveries, seven low forceps, and one midforceps. At the University of Maryland

Hospital prophylactic low forceps extraction is a routine procedure. The midforceps extraction terminated delivery of the patient with severe chronic nephritis.

Six patients were primigravida and seventeen were multigravida.

SUMMARY AND CONCLUSIONS

1. The scalp forceps, although originated fourteen years ago, has found comparatively little popularity, especially in America.
2. A basic description of the instruments and technic employed is given.
3. This method can be used in selected cases of placenta previa, to induce and hasten labor, to insure proper position of the vertex, and to prevent prolapse of the fetal parts or cord. It is believed that it possesses definite superiority over other known methods used for these purposes.
4. The twenty-three cases presented here have led the author to believe that this method should be used more often.

The author wishes to acknowledge the kind cooperation of Dr. L. H. Douglass, from whose service these cases were taken.

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ROENTGEN RAY AND CONSERVATIVE THERAPY IN CHRONIC SINUSITIS*†

Two Case Reports

BENJAMIN S. RICH, A.B., M.D.

BALTIMORE, MD.

This is a preliminary report of two cases of chronic involvement of the paranasal sinuses, with polyposis of the sinus mucosa. The therapy of chronic sinusitis is a much discussed subject among rhinologists, and the methods advanced vary from the too conservative to the ultraradical. Of this particular type of the disease the consensus of opinion has been, and still is, that radical surgery produces the best results. It has also been thought by roentgenologists and rhinologists alike that roentgen therapy is of little value in cases of polyposis of the sinus mucosa, with or without infection. The following two cases demonstrate that it is possible to obtain good results with this method by proper coordination of roentgen and rhinologic therapy.

CASE REPORTS

Case No. 1: A white male, age 44, sea captain by occupation, was seen on May 24, 1940. He complained of severe pain in the left upper jaw, teeth, and eye. The pain had been present at intervals for over a year, but was constant for the past six weeks and becoming gradually more severe. He gave a history of frequent attacks of sinusitis. In 1936 some type of operation, apparently a Caldwell-Luc, was performed on the left antrum by a surgeon in Copenhagen. One year later this was repeated in New York City. He experienced about six months' relief after the first operation and was free of symptoms for only several months following the second operation. There was no history of serious illnesses and his general condition appeared excellent.

An examination revealed the nasal mucosa to be moderately hypertrophic. The breathing space was good, except for a septal deflection on the right which caused some obstruction in the region of the inferior turbinate only. The left middle turbinate was enlarged, congested, and covered with an excess of mucus. Purulent material was not found within the nasal chambers. No polyps or other abnormalities were present. On transillumination the anterior group of sinuses was clear, except the left antrum which was completely dark. There was only slight tenderness on pressure over this sinus. Diagnostic puncture of the left antrum revealed a clear, straw-colored fluid and no pus. A culture was not made. It was thought a cyst of the antral mucosa had been punctured. Repeated examinations showed some involvement of the anterior ethmoid cells. Smears made from nasal secretion showed a few neutrophils and no eosinophils. A roentgen ray examination of the patient was ordered. Figure 1 shows the presence of greatly

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* From the Department of Diseases of the Nose and Throat, School of Medicine, University of Maryland.

† Received for publication October 15, 1940.

thickened mucosa, with polyposis and possible cyst formation. Radical surgery was decided to be the most desirable therapy but the patient refused this on the basis of his previous experiences. Conservative treatment of the ethmoiditis and roentgen therapy to the left antrum were begun. The antrum was irrigated three times at two-

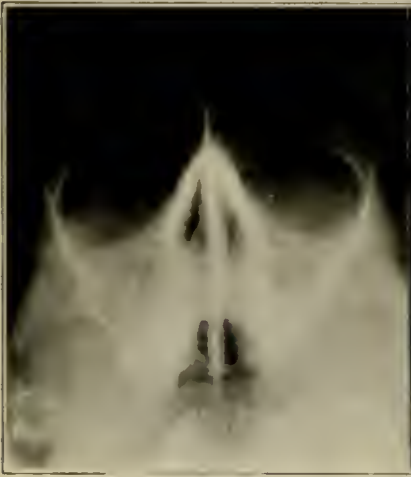
Fig. 1

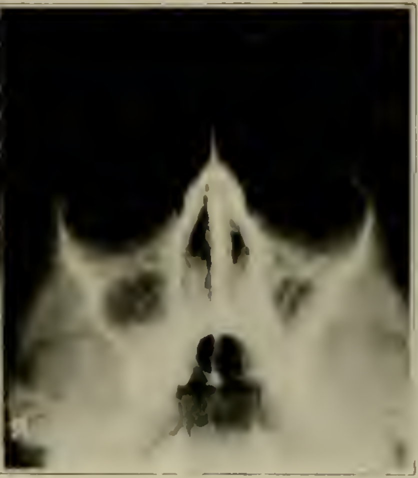
Fig. 2

Fig. 1. A. J. 5/24/40. Before roentgen therapy and after antral irrigation, left antrum involved.

Fig. 2. A. J. 9/6/40. Three months after roentgen therapy was completed.

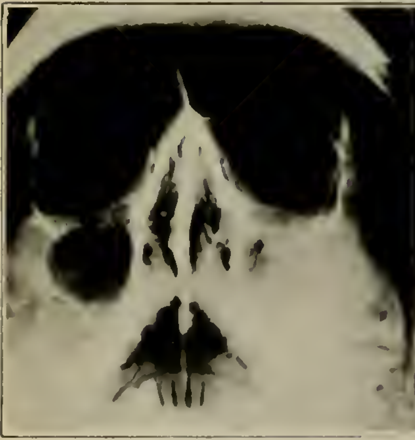
Fig. 3

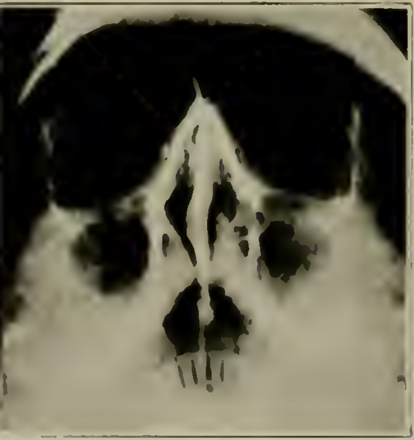
Fig. 4

Fig. 3. A. W. 7/24/40. Before roentgen therapy. Both antra, ethmoids, and left frontal involved.

Fig. 4. A. W. 9/6/40. One month after roentgen therapy was completed.

day intervals and no purulent material nor straw-colored fluid was obtained, the washings returning perfectly clear. Roentgen therapy was begun on May 31, 1940 and completed on June 10, 1940. The patient was symptom-free before the series was completed. He returned for a follow-up examination on September 6, 1940, at which time the rhinologic findings were negative and he was still symptom-free. The roentgenogram taken at this time is shown in Figure 2.

Case No. 2: A white schoolboy, age 17, was treated because of severe hronchitis. The boy had his tonsils and adenoids removed several years previously on account of constant head colds, but this did not prevent subsequent frequent attacks. During the winter of 1939–1940 he had many colds, with thick postnasal discharge and a marked productive cough. However, he was not sufficiently ill to remain out of school. In May, 1940 he developed another cold with the above symptoms, which were still present when seen on July 24, 1940. At this time the examination revealed congestion of the nasal mucosa, mucopurulent discharge in the middle meatus and on the floor bilaterally. The antra, anterior ethmoids and left frontal sinuses were cloudy on transillumination. The nasopharynx was free of excess lymphoid tissue and there was some congestion of the pharynx, with marked mucopurulent postnasal discharge. The tonsils were removed; the hypopharynx was congested and the larynx normal. Smears made from nasal secretion showed many neutrophils and only an occasional eosinophil. Roentgen examination (Fig. 3) showed thickened mucosa with polyp formation, exudate in both antra, and some clouding of the anterior ethmoids and left frontal sinuses. The antra were irrigated five times, mucopus being obtained in the first three washings; conservative therapy was applied to the ethmoids and left frontal sinuses. Roentgen ray therapy to the antra was started on July 29 and completed on August 8. The patient returned for examination on September 6, 1940. At this time there was still some mucoid postnasal discharge; the roentgen examination is shown in Figure 4. Two weeks after therapy was started the cough ceased. On September 20 the postnasal discharge had disappeared and the patient was symptom-free.

These cases do not indicate that the coordination of roentgen and conservative therapy will cure all chronic sinusitis. There is still some thickened mucosa and polypoid tissue present in both instances, although the patients are entirely free of symptoms. It remains to be proved how long they will retain this greatly improved condition. Patients who have undergone radical surgery do have recurrences, mainly because of subsequent exposure to respiratory infections. The same will unquestionably happen with these cases. This method does not prevent the patient from pursuing his daily occupation while undergoing treatment, and is much less costly. A series of these cases will be reported at a later date with a detailed description of the therapy.

PROCEEDINGS

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ONE-HUNDRED-AND-SEVENTH PROGRAM MEETING

The One-Hundred-and-Seventh Program Meeting was held on Tuesday, October 22, 1940 in Gordon Wilson Memorial Hall. The following program was presented:

"A New Volatile Anesthetic, Cyprome Ether," by Drs. John C. Krantz, Jr., Constance Black, George E. Shannon, Sylvan E. Forman, William E. Evans, Jr. and C. Jelleff Carr, Department of Pharmacology, School of Medicine, University of Maryland.

"Determination of Sulfanilamide and Sulfapyridine in Tungstic Acid Blood Filtrates," by Dr. Emil G. Schmidt, Department of Biological Chemistry, School of Medicine, University of Maryland.

Abstracts of these papers follow.

A NEW VOLATILE ANESTHETIC, CYPROME ETHER*†

DRS. JOHN C. KRANTZ, JR., CONSTANCE BLACK, GEORGE E. SHANNON, SYLVAN E. FORMAN, WILLIAM E. EVANS, JR. AND C. JELLEFF CARR

BALTIMORE, MD.

Cyclopropane and ethyl ether have been used successfully as anesthetic agents for a good many years. This work will describe the chemical synthesis of a hybrid molecule between cyclopropane and ether, and extensive preliminary studies on laboratory animals such as frogs, mice, rats, dogs, cats, and monkeys. It will also cover the results obtained with the administration of this compound for the first time to man and the later experiences with twenty-five additional human anesthesias. The substance referred to as cyprome ether seems to bid fair to take its place alongside of the other generally used volatile anesthetics.

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* From the Department of Pharmacology, School of Medicine, University of Maryland.

† Read at the meeting of the University of Maryland Biological Society, October 22, 1940.

THE DETERMINATION OF SULFANILAMIDE AND SULFAPYRIDINE IN TUNGSTIC ACID BLOOD FILTRATES*†

Emil G. Schmidt, Ph.D., LL.B.

BALTIMORE, MD.

The amino-containing compounds normally found in blood react with sodium beta-naphthoquinone-4-sulfonate only in alkaline solution. However, it was found that certain aromatic compounds, such as sulfanilamide and sulfapyridine, react with this color-producing reagent in acid solution as well. Thus, these drugs can be determined in the presence of the amino acids and other amines normally present in blood merely by controlling the reaction of the solutions.

A drop of N/10 HCl is added to 10 cc. of the routine Folin-Wu tungstic acid blood filtrate and to each of a series of 10 cc. standards containing 0.01 to 0.2 mg. of the drug which is being analyzed. Then 1 cc. of a freshly prepared 0.05 per cent solution of sodium-beta-naphothoquinone-4-sulfonate is added to each tube. They are immediately placed in the dark for an hour. The unknown is matched against the standard to which it most closely matches in a colorimeter. A correction factor must be employed since a certain amount of the drug is lost during deproteinization of the blood. The corrected values obtained by this method check well with the values obtained by Marshall's diazotization procedure.

ONE-HUNDRED-AND-EIGHTH PROGRAM MEETING

The annual business meeting of the University of Maryland Biological Society was held in Gordon Wilson Memorial Hall on November 26, 1940 prior to the Program Meeting. The following officers were elected:

President: Dr. Thomas C. Grubb
Secretary: Dr. Robert H. Oster
Treasurer: Dr. Marion W. McCrea
Secretarial Representative: Dr. Roland Bamford
Councillor for one year: Dr. C. Jelleff Carr

At this meeting the following candidates were elected to membership:

Full membership:
Mr. J. Victor Monke
Dr. Milton S. Sacks
Dr. Dietrich C. Smith

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* From the Department of Biological Chemistry, School of Medicine, University of Maryland.

† Read at the meeting of the University of Maryland Biological Society, October 22, 1940.

Associate membership:
Miss Shirley M. Glickman
Mr. Walter C. Gakenheimer
Mr. Wilson C. Grant

The following papers were read at the Program Meeting:

"The Renal Excretion of Hemoglobin in the Dog," by Mr. J. Victor Monke, Department of Physiology, School of Medicine, University of Maryland.

"Studies on the Histogenesis of the Islets of Langerhans in the Albino Rat," by Dr. Walter L. Hard, Department of Zoology, University of Maryland, College Park, Md.

Abstracts of these papers follow.

THE RENAL EXCRETION OF HEMOGLOBIN IN THE DOG*†

J. Victor Monke, M.S.
BALTIMORE, MD.

The mechanism by which the kidney carries out its excretory function is a double one. Blood plasma passing through the glomerular capsule is filtered across the glomerular membrane into the kidney tubules. In this filtering process the plasma proteins remain behind because, it is believed, the protein molecules are larger than the pores in the glomerular membrane. The epithelial cells lining the kidney tubules recover from the filtered fluid some of the important substances, such as glucose, and return them into the blood stream. In addition to the recovery function, the tubular cells also secrete certain substances from the blood stream into the tubular lumina.

Hemoglobin is a protein, the molecular size of which is like that of the albumin of the plasma proteins. The presence of hemoglobin in the urine under certain conditions has been observed medically for several centuries, but no explanation of the process by which it is excreted adequately has met the demands of the modern concept of the kidney mechanisms.

The experimental data obtained as the result of simultaneous hemoglobin and creatinine renal clearance studies indicate that hemoglobin is eliminated by the kidney at a rate which is 3 per cent of the creatinine clearance. A definite renal threshold exists for hemoglobin at a plasma level of about 100 mg. per 100 cc. plasma. Below this level hemoglobinuria does not occur.

It is suggested that the glomerulus permits the filtration of hemoglobin in amounts directly dependent upon plasma concentration. However, only 3 per cent of all the pores of the membrane are electrostatically large enough to permit the passage of an undissociated hemoglobin molecule. Of that hemoglobin which passes down the tubule a relatively constant, though small amount, is recovered by the tubules by a process not unlike that of phagocytosis found elsewhere in the body. An average value for this athrocytic capacity in a medium-sized dog is 2 mg. of hemoglobin per minute.

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* From the Department of Physiology, School of Medicine, University of Maryland.

† Read at the meeting of the University of Maryland Biological Society, November 26, 1940.

STUDIES ON THE HISTOGENESIS OF THE ISLETS OF LANGERHANS IN THE ALBINO RAT*†

Walter L. Hard, Ph.D.

COLLEGE PARK, MD.

The origin of the islets of Langerhans and the differentiation of their cellular elements have been studied throughout embryonic and early postnatal periods of development. In the embryo the islets develop by two distinct methods, as follows:

1. By differentiation of a portion of the primitive pancreatic cord at a time beginning late in the twelfth day and continuing through the fifteenth day.
2. By differentiation of individual cells along the primitive pancreatic tubules with a subsequent increase in mass by differentiation of adjacent cells along the tubule and by mitotic division of the differentiated cells. The majority of the islets are formed by this method and the differentiation occurs most rapidly between the seventeenth and twentieth days.

Scattered beta granules are observed in a few cells toward the end of the eighteenth day. Active secretion, as indicated by polarization of the beta cells occurs during the twentieth day. By the twenty-second day a majority of the cells are well filled and conspicuously polarized. Variable numbers of cells at the periphery of the islet show no granulation. Based somewhat on nuclear characteristics these may be considered alpha cells, but their secretory granules do not appear until early postnatal stages.

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* From the Department of Zoology, University of Maryland, College Park, Md.

† Read at the meeting of the University of Maryland Biological Society, November 26, 1940.

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The names listed above are officers for the term beginning July 1, 1940 and ending June 30, 1941

ITEMS

DR. C. H. HALLIDAY IS NAMED ASSISTANT HEALTH DIRECTOR

Dr. C. H. Halliday, for eleven years State epidemiologist, has been named assistant director of the State Department of Health, a title that has been conferred only once before in the history of the department.

This action was taken with the unanimous approval of the Board of Health at the request of Dr. Robert H. Riley, the director, who is the other man to have held the title of assistant director.

Dr. Halliday has had experience in public health work in many parts of the world and is regarded as one of the nation's leading authorities on the control of epidemics.

In 1905, a year after he graduated from the College of Physicians and Surgeons in Baltimore, he enlisted with the United States Coast and Geodetic Survey as a medical officer, going first to Alaska and then to the Philippines. In the Philippines he joined the Army Medical Corps as a lieutenant. He was on active duty in the field for seven years, then became superintendent of the Zamboanga Hospital. He left the island hospital in 1916 to join the British Army's Medical Corps. When the United States entered the first World War he was transferred to the service of his own country.

He emerged from the war with the rank of major. At present he holds a commission as full colonel in the Medical Corps Reserve.

After the World War, Dr. Halliday saw service in Poland with that country's ministry of Health. Then he became a medical inspector for the American Red Cross.

Back in the United States, he was with the Minnesota State Board of Health, the United States Public Health Service, and the California Health Department before returning to Maryland.

Dr. Halliday is not only the State epidemiologist here, but also director of the bureau of communicable diseases and head of the work done for crippled children.

It is expected that Dr. Halliday's new title will be especially valuable in his future dealings with the Army authorities who are operating the enlarged camps in Maryland. The State Health Department will have much work to do, in cooperation with the Army, in keeping the nonmilitary areas adjacent to the camps free from disease and bad sanitary conditions. This work can be expedited if the State Department has not only a man with authority to act on his own initiative, but a man who also holds the rank of colonel.

MICHIGAN HOSPITAL ERECTED AS MONUMENT TO UNIVERSITY OF MARYLAND GRADUATE

The Addison Community Hospital, built largely by volunteer labor and at a cost of $15,000, was dedicated in Addison, Michigan on November 10, 1940 as a monument to Dr. Bowers H. Growt, a graduate of the University of Maryland.

The people of Addison had a hospital of sorts since Dr. Growt first settled there—a hospital believed to be the first of its kind in rural Michigan—originally located in a rented store building and then in a brick farmhouse.

Dr. Growt, now 49 years old, attended Baltimore City College and received his degree of medicine from the University of Maryland in 1916, after which he served overseas as an officer in the Medical Corps of the United States Army. He was gynecologist in the Maryland General Hospital when, in 1920, he decided to start the practice of medicine at Addison. He came to Michigan expecting to establish himself in a populous city. Addison was a small rural community with no hospital nearby and few natural advantages for a city-trained physician. This would have been disheartening to any doctor, but Dr. Growt started in to make the best of what he had.

Addison folk responded in kind. Their loyalty to Dr. Growt was manifest in the community support of his hospital project when it was little more than a two-bed infirmary adjoining his office. In trying to establish an adequate health center the doctor was not helped by Government aid or large philanthropy, but by his farm neighbors and former patients. They staged benefit shows, dances, church suppers, and rummage sales to help swell the building fund. Those who could not give money contributed their time and labor. One of the young men who laid bricks hour after hour in the hot summer sun, without accepting a cent of pay, was a boy whose birth Dr. Growt had assisted when he first came into the community.

When neighbors learned that the operation of the farmhouse hospital quarters was taking some of the doctor's personal funds, the township boards of four adjacent townships voted an appropriation to help meet the burden. They later named a community hospital board to take this load off the doctor's shoulders entirely.

A number of important personages attended the hospital dedication and spoke in tribute to Dr. Growt. However, there was none present more important to Addison than Dr. Bowers H. Growt himself, their "country doctor."

BOARD OF TRUSTEES OF THE BRESSLER RESEARCH ALUMNI FUND AWARDS GRANTS

The Board of Trustees of the Bressler Research Alumni Fund met in the library of the Bressler Building on Thursday, October 31, 1940. Dr. J. Mason Hundley, Jr. presided. Those present were Drs. William R. Amberson, Carl L. Davis, John C. Krantz, Jr., Maurice C. Pincoffs, and Eduard Uhlenhuth. Dr. Davis was elected Treasurer of the Board of Trustees of the Bressler Research Alumni Fund for the purpose of administering the funds awarded by the Trustees.

The following grants were requested and unanimously approved by the Board. The total sum awarded was $3983.30.

Glenn H. Algire, Department of Medicine, $150, for the study of skin metabolism in hyperthyroidism.

Thomas B. Aycock, Department of Experimental Operative Surgery, $200, to study pre- and postoperative gastric acidity in experimental animals, and the relationship of anemia to total and partial gastrectomies.

George H. Yeager, Department of Experimental Operative Surgery, $300, to study the treatment of the appendiceal stump.

Edward G. Boettiger, Department of Gynecology, $700, for hormone studies pertaining to menstrual dysfunctions, that is, menopause, amenorrhea, dysmenorrhea, oligomenorrhea, sterility and ovulation, and the effect of hysterectomy on the hormone balance of the ovaries.

Dietrich C. Smith, Department of Physiology, $100, to continue the study of the effect of certain vitamins on metabolism.

Robert H. Oster, Department of Physiology, $218.65, for the determination of the existence and characteristics of after-potentials in striated muscle, and a study of electro-encephalograms as obtained in the cat during normal alkalosis states to determine the effect of change in blood ions on neurone activity.

James Toman, Department of Physiology, $207.65, for the study of the Flicker potentials and the alpha rhythm in man.

William R. Amberson, Department of Physiology, $250, to study the preparation of dried hemoglobin in the hope that this material, properly sterilized and in suitable containers, may have some application in emergency transfusion work in time of war.

O. G. Harne, Department of Histology and Embryology, $475, for the study of the life duration of the red blood cell in primates.

LeRoy W. Tilt, Jr., Department of Histology and Embryology, $132, for study of the structure of the alveoli of the lung of the rabbit.

Eduard Uhlenhuth, Department of Gross Anatomy, $850, for study of the experimental stimulation of the anterior lobe and to investigate finer structures of the inner ear of mammals which are known to have certain peculiarities of the sense of hearing, such as bats, moles, and certain rodents.

John C. Krantz, Jr., Department of Pharmacology, $400, for the determination of nitrites in normal human and pathological human blood, and in addition a study of the influence of diet upon the nitrite content of dog's blood and the correlation of blood nitrite concentrations, if possible, with hypertensive states.

According to the stipulations of the Trustees these monies were granted as aids in research and not to be used for salaries of fellows engaged in the work.

Respectfully submitted,
JOHN C. KRANTZ, JR., *Secretary.*

Dr. Arthur M. Shipley, Professor of Surgery, spoke on "The Surgical Problems that Arise in General Practice" at the monthly meeting of the Baltimore County Medical Association which was held on November 20, 1940.

Dr. J. Mason Hundley, Jr., Professor of Gynecology, and Dr. Edward A. Looper, Professor of Diseases of the Nose and Throat, delivered addresses at the meeting of the Maryland Academy of Medicine and Surgery held on November 19, 1940. Dr. Hundley's subject was "Discussion and Treatment of Lesions of the Cervix." Dr. Looper spoke on "Cancer of the Larynx."

Dr. Maurice Feldman, Assistant Professor of Gastro-Enterology, participated in the program arranged for the meeting of the Radiological Society of North America in Cleveland, Ohio on December 4, 1940. His subject was "A Radiological Consideration of the Normal Mucosa of the Duodenum."

Dr. Philip Adalman (U. of Md. 1931), 1018 East 163rd Street, Bronx, New York, has been granted the certificate of the American Board of Ophthalmology.

Dr. Remo Fabbri (B.M.C. 1909) of Norristown, Pennsylvania has been appointed a member of the Selective Service, Local Board No. 2, of Norristown.

Dr. Walter D. Wise has been appointed as a surgical member of the Board of Editors of the Bulletin of the School of Medicine, University of Maryland. Dr. Wise is Professor of Surgery and a member of the Medical Council of the School of Medicine, and Surgeon-in-Chief and Chairman of the Board of Governors of Mercy Hospital.

At the meeting of the Maryland Academy of Medicine and Surgery which was held on December 17, 1940 the scientific part of the program was conducted by Dr. Arthur M. Shipley, Professor of Surgery, and Dr. C. Loring Joslin, Professor of Pediatrics. Dr. Shipley's subject was "The Acute Gallbladder," and Dr. Joslin spoke on "Acute Laryngotracheobronchitis."

Dr. Norbert C. Nitsch (U. of Md. 1913) has been appointed as a physician to the Police Department of Baltimore City.

One hundred specimens of miniature (toy) books, small scale printing, bindings and illustrations, arranged in eight specially lighted glass cases, were exhibited at the Enoch Pratt Free Library by Mrs. Ruth Lee Briscoe, of the Library of the School of Medicine, from October 14 to November 14, 1940. Mrs. Briscoe also spoke on this subject over a local broadcasting station.

Ten members of the Alumni Association attended the banquet of the Southern Medical Association which was held on November 14, 1940 at the Brown Hotel, Louisville, Kentucky. Those who were present at the dinner which was tendered during the annual meeting of the Association were:

Dr. R. S. Griffith, Waynesboro, Va., P. & S. 1886
Dr. W. T. Wootton, Hot Springs, Ark., U. of Md. 1899.
Dr. George D. Johnson, Spencer, W. Va., P. & S. 1908
Dr. H. M. Robinson, Baltimore, Md., U. of Md. 1909
Dr. T. R. Bowers, Bristol, Va., U. of Md. 1923
Dr. F. A. Holden, Baltimore, Md., U. of Md. 1924
Dr. Joseph M. Frehling, Louisville, Ky., U. of Md. 1924
Dr. M. Martyn Kafka, Fort Knox, Godman Field, Ky., U. of Md. 1924
Dr. J. R. Godbey, Charleston, W. Va., U. of Md. 1935
Dr. William Platt, Lexington, Ky., U. of Md. 1940

Dr. Griffith, a graduate of 1886, was escorted to the stage and presented as the oldest alumni of any school present.

OBITUARIES

HARRY M. STEIN, M.D.

The untimely death of Dr. Harry M. Stein, Professor of Clinical Medicine, came as a grievous shock to his colleagues and to his wide circle of friends in the medical profession, as well as to his many devoted patients. Though it was realized that he had been in ill health for some months, few besides his family had been aware of the rapid progress of the malignant form of arterial hypertension which ultimately caused his death. He leaves behind him his wife, the former Miss Marguerite Risley, and his sister, Miss Rita Stein.

Dr. Stein was born in Baltimore on January 26, 1892. He attended the public schools of this city and then entered the Baltimore City College, from which he graduated in the Class of 1910. Four years later, in 1914, he received his diploma from the University of Maryland School of Medicine and was appointed as house officer in the Tuberculosis Division of the Baltimore City Hospitals under Dr. Gordon Wilson. This was the beginning of an intimate association and a warm friendship lasting until Dr. Wilson's death. It was the beginning also of a lifelong interest in the subject of tuberculosis. With Dr. Stein at the City Hospitals in those days were his classmate and closest friend, Dr. Charles Habliston, and also Dr. Arthur M. Shipley, Dr. W. H. Toulson, Dr. M. C. Pincoffs, and others with whom his future work in the Medical School was to be closely connected. The following year Dr. Stein returned to the University Hospital as resident in medicine and after completing this service he was appointed medical superintendent of the hospital, a signal honor for a man of his age.

With the outbreak of war in 1917 Dr. Stein resigned his position to join the University of Maryland Unit, Base Hospital No. 42, as a First Lieutenant in the Medical Division under Major Cary Gamble. He served with the Unit overseas chiefly near Bazouille, France, and came home with a fund of experiences both of the darker and lighter sides of wartime days, which he could be induced in after years to recount to the delight of his friends. Among his gifts was that of seeing the humorous side of the most trying circumstances and few who heard him could forget his tales, for example, that of his subterfuges to escape routine therapy when he developed pneumonia. At Bazouille also with Base Hospital No. 42 was Miss Marguerite Risley who served on the nursing staff. When the Base Hospital came home Dr. Stein again became medical superintendent of the University Hospital, but a year later resigned this position to enter private practice. In October, 1921 he was married to Miss Risley.

He was appointed by Dr. Gordon Wilson as chief of the medical dispensary and gave his time and energy freely to reorganize and develop this clinic. Here he first showed his great ability to develop in younger men the keen interest he himself always possessed in clinical medicine. He soon had a wide following in the School, and as the years went on and his former students scattered over the State his reputation grew as a teacher and a brilliant internist. His importance to the Department of Medicine was witnessed by his rapid rise to the rank of Professor of Clinical Medicine and his appointment as chief of the medical service in the University Hospital. This position he held until he accepted the appointment, as Dr. Habliston's successor, to be the chief of the Tuberculosis Division in the Baltimore City Hospitals. Even then he retained a medical service on the wards of the new University Hospital until his death.

During these twenty years his working power was phenomenal. In addition to his ward teaching, his lectures and clinics, he developed an admirable clinic for the treatment of diseases of the chest at the City Hospitals, closely supervised his ward in the University Hospital, and served for a number of years as chief physician at St. Josephs Hospital. Aside from all this he had a large practice in internal medicine and was widely sought as a consultant.

It was through his quality as a teacher that he made an impress on the medicine of his time. He was at his best at the bedside. Incisive, witty, sensitive to the mood both of the patient and of his audience, always practical in his point of view, he taught both by precept and example how to arrive at the gist of the problem in hand. He was never radical, he was not impressed by unsupported theory, and he had a clinical fifth sense which made him see the important facts in the midst of unessential details. He had wide interests in the whole field of medicine, but a special proficiency in the diseases of the lungs and in diabetes. What he taught to his students will live on in their practice to the benefit of many who will be unaware of their debt to him.

It is not remarkable that his activities left him little time for research, or for writing or for the attending of many medical meetings. These were secondary matters to him, while his work and his own studies demanded and obtained his full time.

To those who have not known him it will not be possible to describe the unusual and attractive personality of this gifted man. He was unpredictable, often gay and full of life and sometimes retired, silent and withdrawn into himself. He was constantly self-depreciating and humorous over his supposed failings, but in times of emergency he was serious and courageous, and spoke with authority. He was loyal to his friends and capable of great friendship. The death of Charles Habliston, who was closer to him than any other man, saddened his later years. Those who witnessed the way in which he spent his strength to make his friend's long illness more bearable saw revealed the tenderness and affection which lay beneath the surface.

In the death of Dr. Harry M. Stein the Faculty of the University of Maryland has lost not only a brilliant teacher but a true man who will be long remembered and missed.

M. C. Pincoffs.

RANSOM LEE CARR, M.D.

Dr. Ransom Lee Carr, B.M.C. 1907, physician and legislator of Duplin County, North Carolina, died on October 17, 1940 at Rosehill, North Carolina at the age of sixty-two.

Dr. Carr received his early education at Rockfish Academy and Davidson College, the latter being known at that time as the North Carolina Medical College. Afterward he attended the Virginia Medical College and the Baltimore Medical College, graduating from the last-named institution in 1907.

As a small town and country physician of the old type Dr. Carr practiced night and day for thirty-two years, and during most of this time he was the only physician of his village and countryside. He served two years as Duplin County health officer and was considered an eminent general diagnostician and a specialist in certain diseases. He conducted the first typhoid clinic ever held in the county.

A Presbyterian elder and Sunday school superintendent, Dr. Carr was also fraternally connected with a number of orders, and had served as secretary of the local Chamber of Commerce. In 1911 he established a county newspaper at Rosehill. He was county food administrator during the World War.

MARTIN J. HANNA, M.D.

Dr. Martin J. Hanna, aged 53, died in the Maryland General Hospital in Baltimore on December 2, 1940.

Dr. Hanna was born in Howard County, received his education in the county public schools, and graduated from the Southern Medical Department in Sewanee, Tennessee in 1908. Upon graduation he started to practice in Baltimore and then moved to West Virginia as a health officer. During the World War he was a captain in the Medical Corps with the American Expeditionary Force in France. After the war he returned to Baltimore and opened his office at 1822 West Baltimore Street, where he practiced and lived until his death.

Most of Dr. Hanna's time for many years had been spent in industrial practice. He was physician for the American Sugar Refinery, and had been on the staffs of the South Baltimore General and Franklin Square

Hospitals. For several years he was coroner in the Southwestern district. In addition, Dr. Hanna was connected with the Department of Anatomy and taught gross and microscopic anatomy. He was an exceptionally good teacher and very popular with the students.

J. WILLIS MARTIN, M.D.

Dr. J. Willis Martin, U. of Md. 1917, aged 45, died at his home in Eastport, Maryland on November 5, 1940.

After receiving his degree in medicine Dr. Martin enlisted in the Medical Corps of the United States Army and served overseas. Before his death he was chief of staff at the Emergency Hospital in Annapolis, Maryland, and a member of the American College of Surgeons.

E. E. NOEL, M.D.

Dr. E. E. Noel, P. & S. 1884, aged 81, died in a hospital in Huntington, West Virginia on July 18, 1940.

Dr. Noel was born at Green Sulphur Springs and educated in the public schools of Summers County and Concord State College in Athens, West Virginia. He practiced in West Virginia since the year of his graduation and was one of West Virginia's oldest practicing physicians, not only in age but in years of active service in his profession. Despite his advanced age Dr. Noel was active in the practice of medicine up to the time of his death.

WILBUR MOATE SCOTT, M.D.

Dr. Wilbur Moate Scott, U. of Md. 1912, aged 51, died at his home in Milledgeville, Georgia on October 31, 1940.

After graduation from the School of Medicine he did postgraduate work at Johns Hopkins University. He then returned to Devereaux, Georgia, where he practiced until the first World War, at which time he enlisted in the Medical Corps of the United States Army and served overseas. After the war he returned to Devereaux and resumed his practice. In 1923 he moved to Milledgeville, established the Scott Hospital, and continued to practice until his death.

Dr. Scott took an active interest in the affairs of the American Legion and was a past commander of that organization. In addition, he took an active interest in the social, religious and political affairs of his community.

Armstrong, Louis Woodruff, Danville, Ind.; class of 1900; aged 64; died, September 19, 1940, of angina pectoris.

Ayres, Charles C., Shawsville, Md.; class of 1914; aged 48; died, December 9, 1940, in the Maryland General Hospital of Baltimore, of cerebral hemorrhage.

Battle, John T. J., Greensboro, N. C.; P. & S., class of 1884; aged 81; died, September 30, 1940.

Baxter, Enoch Wilson, Moyock, N. C.; P. & S., class of 1887; aged 79; died, August 10, 1940.

Berge, William Henry, Scranton, Pa.; P. & S., class of 1893; aged 71; died, July 14, 1940, of coronary thrombosis.

Blachly, Frank L., Sr., Moline, Ill.; P. & S., class of 1881; aged 80; died, July 27, 1940, of mesenteric thrombosis.

Bradley, Hugh F., Jarrettsville, Md.; class of 1897; aged 75; died December 5, 1940.

Buxton, Gilbert Franklin, Baltimore, Md.; P. & S., class of 1907; aged 63; died, May 6, 1940, of myocarditis.

Cotter, Timothy Francis, Haverhill, Mass.; B.M.C., class of 1906; aged 57; died, July 3, 1940, of carcinoma of the rectum with metastases.

Crofts, Nicholas Matthew, North Adams, Mass.; B.M.C., class of 1898; served during the World War; aged 74; died, September 17, 1940, of coronary thrombosis.

Dailey, Cornelius M., Carnegie, Pa.; B.M.C., class of 1905; aged 63; died, August 19, 1940, of glomerular chronic nephritis.

Foard, William Roe, Cumberland, Md.; B.M.C., class of 1903; aged 58; died, August 4, 1940, in the Allegany Hospital, of injuries received in an automobile accident.

Frazier, Henry Bowen, Bluefield, Va.; P. & S., class of 1897; aged 68; died, August 9, 1940.

Gately, Joseph Edward, Baltimore, Md.; class of 1902; served during the World War; aged 60; died, July 21, 1940, of cerebral hemorrhage, embolism and coronary infarction.

Hall, Frank Marion, Sylvan Beach, N. Y.; B.M.C., class of 1897; aged 68; died, September 6, 1940.

Hanover, Rudolph, McKees Rocks, Pa.; B.M.C., class of 1906; aged 62; died, August 1, 1940, in the Montefiore Hospital, Pittsburgh.

Highberger, William T., Maysville, W. Va.; class of 1883; aged 80; died, September 6, 1940.

Hobeb, Albert Salomon, Rutherford, N. J.; class of 1921; served during the World War; aged 47; died, September 13, 1940, of chronic myocarditis.

Hopkins, Harry Daniel, Waterbury, Vt.; B.M.C., class of 1901; aged 62; died, October 2, 1940, of coronary thrombosis.

Leonard, William Joseph, Provincetown, Mass.; P. & S., class of 1896; served during the World War; aged 70; died, July 25, 1940.

Lewis, Howard Davis, Sunbury, Pa.; class of 1900; aged 62; died, October 2, 1940.

Little, DeWillis, Appleton, Minn.; P. & S., class of 1883; aged 80; died, August 11, 1940, of coronary occlusion.

Matthews, Andrew Aldridge, Spokane, Wash.; class of 1900; veteran of the Spanish-American and World Wars; aged 62; died, September 23, 1940, in the Swedish Hospital, Seattle, of carcinoma of the stomach.

Neal, Joe W., Walnut Cove, N. C.; P. & S., class of 1889; aged 76; died, August 2, 1940, of lobar pneumonia.

Norton, John Charles, Baltimore, Md.; class of 1912; aged 51; died, November 9, 1940, of a heart attack.

O'Brien, William Aloysius, Jr., Passaic, N. J.; class of 1936; aged 33; died, September 13, 1940, in St. Vincent's Hospital, New York, of acute miliary tuberculosis.

Park, H. L., Union City, Tenn.; P. & S., class of 1886; aged 85; died, July 11, 1940, of chronic myocarditis.

Peckham, William David, Utica, N. Y.; B.M.C., class of 1897; aged 65; died, September 9, 1940, of coronary thrombosis.

Posey, David C., Christiana, Pa.; B.M.C., class of 1908; aged 60; died, July 6, 1940, of coronary thrombosis.

Ransom, Herbert LeRoy, Pittston, Pa.; class of 1910; served during the World War; aged 64; died, July 22, 1940.

Rogers, James Rufus, Raleigh, N. C.; P. & S., class of 1886; aged 73; died, July 5, 1940, of acute mesenteric thrombosis and diabetes mellitus.

Rowe, Michael James, Bridgeport, Conn.; P. & S., class of 1896; veteran of the Spanish-American War; aged 73; died, September 30, 1940, of cystitis, pyelitis, bladder and kidney calculi.

Sawyer, Charles Judson, Windsor, N. C.; P. & S., class of 1895; aged 72; died, July 28, 1940, of coronary thrombosis.

Smith, J. S., Radford, Va.; P. & S., class of 1887; aged 78; died, July 23, 1940, of myocarditis.

Smith, Thomas J., Cranston, R. I.; P. & S., class of 1884; aged 81; died, November 21, 1940.

Speight, Richard H., Jr., Rocky Mount, N. C.; class of 1901; aged 61; died, July 31, 1940, of coronary thrombosis.

Swartzwelder, Wallace Ray, York, Pa.; class of 1927; aged 40; died, in September, 1940.

Walker, James, Thomas, Crowder, Miss.; P. & S., class of 1886; formerly mayor; aged 75; died, July 22, 1940.

Woods, George Brinton, Curllsville, Pa.; P. & S., class of 1887; aged 77; died, September 29, 1940, of cerebral hemorrhage.

BULLETIN
OF THE
SCHOOL *of* MEDICINE
UNIVERSITY OF MARYLAND

1807 · 1856 · 1920

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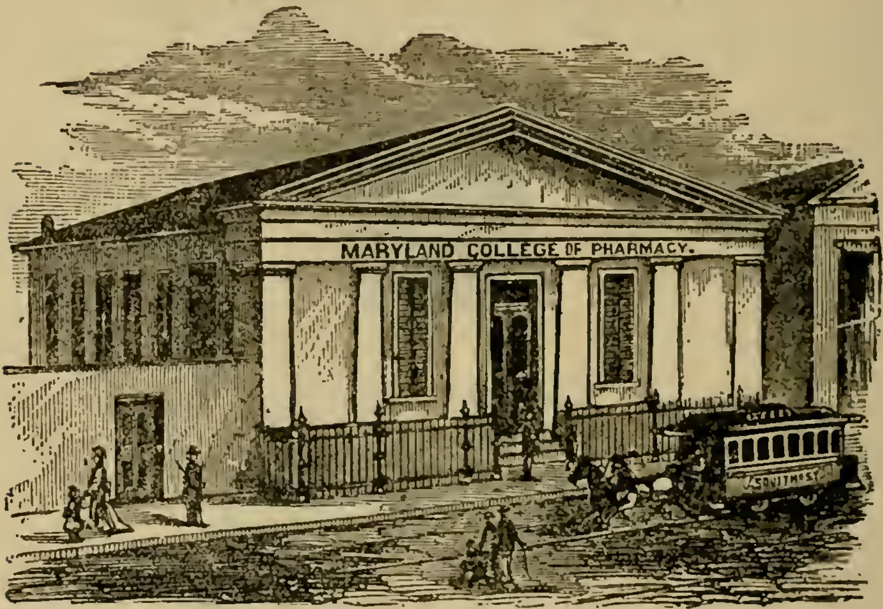
CONGRATULATIONS TO THE SCHOOL OF PHARMACY ON ITS ONE HUNDREDTH ANNIVERSARY

1841 - 1941


MARYLAND COLLEGE OF PHARMACY.
S. SMITH ST.

THE history of the University of Maryland is a splendid record of solid progress in the most vital fields of education. Since the founding in 1807 of the College of Medicine of Maryland, the first unit of the present group to be established, the University has made many important contributions to the general education and welfare of our citizens, and this is particularly true of its professional schools in Baltimore, most of which are a hundred or more years old.

In 1940 the School of Dentistry, the oldest dental school in the world, celebrated its centennial. This year the School of Pharmacy is observing the one hundredth anniversary of its founding as the Maryland College of Pharmacy. Law had its beginning in 1813 but regular instruction was not organized until 1823. The School of Nursing was founded more than half a century ago by a pupil of the world-renowned Florence Nightingale. The vision of "Our Founders" was finally fulfilled in 1920, when these Baltimore schools were merged with the Maryland State College, founded in 1856, to form the present University of Maryland.

That the University may long and honorably continue "to produce the most beneficial results to our State by instilling into the minds and hearts of its citizens the principles of science and good morals" is our fervent desire.

BULLETIN
OF THE
SCHOOL OF MEDICINE
UNIVERSITY OF MARYLAND

Vol. 25 APRIL, 1941 No. 4

NEW TESTS OF KIDNEY FUNCTION*†

WILLIAM R. AMBERSON, Ph.B., Ph.D.
BALTIMORE, MD.

NEW CONCEPTS OF KIDNEY CLEARANCE

The diagnosis of the nature and severity of renal disease has long been a prime interest of the medical profession. Various routine clinical tests have been developed and are widely used as diagnostic aids. They include such procedures as the determination of urea clearance, of the rate of excretion of injected phenolsulphonphthalein, or of the variations in volume and specific gravity of the urine. They may take the form of the measurement of nonprotein nitrogen, urea or creatinine concentrations in blood plasma. Such tests are of considerable value in clinical work, but they give only general and partial information concerning the state of the kidney, and throw little light upon the particular site of injury or the special function disturbed by the disease. In recent years new tests of kidney function have been proposed which may permit more accurate and detailed diagnosis. So far these procedures have been used mainly in research laboratories where the chief interest has been in normal renal physiology. Attention is now being directed to possible clinical applications. It is the purpose of this review to describe some of the basic technics involved and to summarize the recent literature.

In 1926 Rehberg (19) proposed the use of exogenous creatinine to determine the magnitude of the glomerular filtration. He pointed out that the ratio of urinary creatinine to plasma creatinine is higher than that found for any other normal urinary constituent. He argued that it is probable that creatinine is readily filtered in the glomerulus, and is neither reab-

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*From the Department of Physiology, School of Medicine, University of Maryland.

†Received for publication February 27, 1941.

sorbed nor secreted by the cells of the tubules. It becomes concentrated in the urine, therefore, because of the reabsorption of most of the water by the cells of the tubules. From its concentration ratio, he believed, it is possible to calculate glomerular filtration rate at any period if the minute volume of bladder urine is simultaneously measured.

This simple principle of Rehberg has been accepted in all recent work and is valid for such animals as the dog, rabbit, sheep and seal. Unfortunately, it has been found that in man, the anthropoid ape and the chicken, exogenous creatinine is excreted through the tubule cells in addition to being filtered in the glomerulus. Some workers [Popper, Mandel, and Mayer (18), and Steinitz and Türkand (31)] now maintain that endogenous creatinine, if determined by improved analytical methods, is an accurate measure of glomerular filtration rate, but this claim is denied by Smith, Finkelstein, and Smith (28) who report such variability in results that trustworthy calculations are impossible.

In the growing literature of this field the term "clearance" has come to have a precise meaning, which the reader must understand. In this more exact signification the word was first employed by Möller, McIntosh, and Van Slyke (17) in connection with their studies of urea excretion. They defined urea clearance as *the volume of blood which one minute's excretion of urine suffices to clear of urea.* Since tests are usually made on plasma rather than on whole blood, clearance is now more usually defined as a plasma volume. Stated most generally, the clearance for any substance may be defined as the "volume of plasma containing the amount of that substance which is excreted per minute." Alternatively, it may be defined as "the minimum volume of plasma required to furnish the quantity of substance excreted in the urine in one minute's time." For most substances no single cubic centimeter of plasma is completely cleared in any one passage through the glomeruli. A few substances exist which are completely cleared in one passage and are now used to measure plasma flow, a technic which will be considered shortly.

The reader should also familiarize himself with a simple mathematical expression, valid for the clearance of any substance. It includes the special case of any substance which is freely filtered in the glomeruli, but neither excreted nor reabsorbed by the tubules (Rehberg's principle):

$$C = \frac{U}{P} \cdot V \qquad \left(\text{or } \frac{UV}{P}\right)$$

Where C = clearance of any substance
U = concentration of that substance in the urine
P = concentration of that substance in the plasma
V = volume of bladder urine excreted per minute.

Thus, if, in the dog, plasma creatinine has a value of 10 mg. per cent, urinary creatinine a value of 600 mg. per cent, and urine flow per minute is 1 cc., then

$$\begin{aligned}\text{Creatinine clearance} &= \frac{600 \cdot 1}{10}\\ &= 60 \text{ cc. of plasma per minute.}\end{aligned}$$

In this animal creatinine behaves as the ideal substance which is neither absorbed nor excreted by the tubules after being freely filtered in the glomerulus. Its clearance therefore measures the rate of glomerular filtration from the plasma. That rate is also 60 cc. per minute.

It must be noted that kidney clearances, stated in this manner, do not refer to any particular quantities of the substance in question. The concentrations in plasma and urine may be low or they may be high. Only the ratio of the two values is important. Quite a few substances give exactly the same calculated clearance volumes at high plasma levels as at low. The ability of the kidney to excrete is thus stated in a more general, yet more precise manner than if actual total quantities excreted are used.

THE INULIN METHOD

Since Rehberg's original suggestion many other investigators have sought to discover substances other than creatinine which fulfill the requirements of an ideal renal "yardstick." These requirements have been summarized by Homer Smith (24) in a monograph review of this field, to which the reader is referred for more detailed information. He and his associates (14) at first believed that nonmetabolized sugars, such as xylose and raffinose, fulfilled the requirements. Later it was discovered simultaneously in two laboratories [Richards, Westfall, and Bott (21), and Shannon (22)] that the polysaccharide, inulin, gives clearances which are about 25 per cent higher than xylose clearances.

Further studies of renal function with inulin have established it as a substance which, in man at least, closely approaches the ideal yardstick. Its free filtration in the glomeruli is evidenced by several lines of work. In the frog, where glomerular filtrate can be directly collected, the inulin concentrations in plasma and urine are known to be identical. Richards (20) has recently reviewed the amphibian studies. The rate of excretion of inulin in the urine (UV) increases over wide limits in simple direct proportion to the plasma concentration (P). This fact has recently been established in great detail by Miller, Alving, and Rubin (15) for low inulin plasma levels. In other words, the clearance $\left(\frac{UV}{P}\right)$ is independent of the plasma concentration, as it should be if there is neither excretion nor reabsorption in the tubules. After administration of adequate doses of the drug, phlorizin, which prevents tubular reabsorption of glucose, the inulin and glucose clearances are identical—a further indication that inulin is not reabsorbed.

Inulin has a molecular weight of approximately 5000, and must consist of 32 hexose molecules. The molecule is elongate, so that in diffusion through membranes it behaves as if its molecular weight were about 15,000. It is close to the upper limit of size which still permits ready passage through the glomerular membranes. This large size may be mainly responsible for the absence of tubular reabsorption or excretion. Inulin is small enough, however, to pass readily across the endothelial walls of the capillaries. After administration, therefore, it diffuses out of the plasma into all of the extracellular water. This circumstance, however, does not in any way interfere with its value in renal studies.

The use of inulin in experimental and clinical work is facilitated by the recently introduced diphenylamine method of Corcoran and Page (7), and of Alving, Rubin, and Miller (2). Fermentable carbohydrate is removed by the incubation of urine or deproteinized plasma with yeast. After the addition of an acid-alcohol diphenylamine reagent, the solution is heated to hydrolyze the inulin. Levulose derived from the inulin reacts with the diphenylamine to give a clear blue color, which is read by a colorimeter.

While it is now generally agreed that inulin furnishes a most acceptable tool for renal clearance studies, there are some investigators who suggest the use of alternative substances. Among these may be mentioned (a) the disaccharide, sucrose, which Winkler and Parra (34), and Steinitz (30) find to give clearance values close to inulin figures; (b) sodium ferrocyanide, which in the rabbit and dog clears like inulin according to Gersh and Stieglitz (11), and Van Slyke, Hiller, and Miller (33), but which Miller and Winkler (16) have found to be reabsorbed by human tubules, although Stieglitz (29) believes that ferrocyanide may still furnish a useful clinical test for renal function; and (c) the hexitols, sorbitol, mannitol and dulcitol, and their derivatives which, according to Smith, Finkelstein, and Smith (28) have clearances identical with that of inulin.

CLINICAL APPLICATIONS OF THE INULIN METHOD

The introduction of the new renal functional tests is leading to modifications in the views concerning the urea clearance, probably the most widely used index in diagnosis of renal disease. Möller, McIntosh, and Van Slyke (17) distinguished "standard" urea clearances at rates of urine flow below 2 cc. per minute, and "maximal" clearances at higher rates of flow. Their nomograms are used extensively in clinical laboratories for the quick evaluation of the percentage of average normal function present in any case. Standard clearances are calculated for a flow of 1 cc. per minute on the assumption that clearances in the lower range vary according to the square root of the minute volume of urine. The standard mean normal value for this rate of flow is given as 54 cc. Maximal clearances, with a mean normal value of 75 cc., are considered constant above the "augmentation limit" of 2 cc. per minute.

The validity of this distinction has been rendered doubtful by recent work. Chasis and Smith (4) have not observed a definite point on the urine flow scale above which a constant maximal urea clearance is observed. Clearance values continue to increase slowly as the flow becomes greater and greater. They studied the behavior of inulin simultaneously with the urea determinations and observed a slight rise in inulin clearance at the most rapid flows. Average clearance values read from the data secured from one of their subjects are as follows:

URINE FLOW	UREA CLEARANCE	INULIN CLEARANCE
cc./min.	*cc./min.*	*cc./min.*
.75	48	125
1.00	52	118
2.00	58	115
4.00	62	115
10.00	70	120
16.00	75	130

It is clear from these data that urea, which is known to pass freely into the glomerular filtrate in the same concentration as it occurs in blood plasma (20), must be in part reabsorbed in the tubules. The percentage of reabsorbed urea falls as the urine flow increases, so that its clearances rise. There is some evidence that an active tubular process may be partly responsible for urea reabsorption, similar to the one which is certainly present for glucose. It may be solely responsible at the most rapid urine flows. The greater reabsorption at low urine flows is probably caused by the simple diffusion of an additional fraction of the urea back through the tubule walls into the blood stream, at the time that water is being reabsorbed. It would appear that the tubular walls are not entirely impermeable for urea.

Doubt as to the validity of the calculation of the standard urea clearance has arisen from the work of Chesley (5) who describes a "minimal" urea clearance. He finds that the square root rule fails when urine flows are below 0.5 cc. per minute. Such low flows occur in normal subjects after a thirty to sixty hour food and water fast. They appear sooner in patients with renal disease. A maximal concentration ratio for urea, creatinine, inorganic phosphorus, and other urinary constituents is observed when this critical value is reached—a ratio which is not further increased at slower flows. Below this critical value urea clearances become directly proportional to the urine flow. Chesley concludes that in this low range a reduced glomerular filtration rate, rather than increased tubular reabsorption, is responsible for the diminished urine flow. He thinks that a constant and perhaps maximal proportion of the filtered water is reabsorbed by the tubules. Since low urine flows are encountered in some diseases, his objection to the present routine of calculation for standard clearances by the square root rule deserves attention in clinical laboratories.

When the clinician calls for a urea clearance test he should realize that he is asking for information about a substance which in man is excreted entirely through the glomeruli, which in part escapes from the tubular fluid back into the blood stream, and whose reabsorbed fraction increases as the rate of urine flow diminishes. The exact mechanism of this reabsorption is still in doubt, and mathematical expressions covering the whole range of flow values cannot yet be given. It appears more profitable to work from an empirical curve combining the data of Chasis and Smith (4), and Chesley (5). From their graphs the writer has taken the following mean normal values:

URINE FLOW	UREA CLEARANCE
cc./min.	*cc./1.73 sq. m./min.*
0.1	9
0.2	18
0.3	27
0.4	36
0.5	43
0.75	50
1.0	54
1.5	57
2.0	60
4.0	62.5
6.0	65
8.0	66.5
10.0	68
12.0	73
14.0	78

It will be noted that the clearance at urine flow of 1 cc. per minute is 54 cc. This is identical with the normal mean standard clearance of Möller, McIntosh, and Van Slyke (17). It will also be noted that the average of the values for urine flows from 2 to 14 cc. per minute is 67.5 cc. per minute. This is close to the normal mean maximal clearance of Möller, McIntosh, and Van Slyke, but the figures here suggested have the virtue of indicating the gradual rise in the clearance values over the range in which those authors considered the clearance to be constant. The "percentage of normal function" at any urine flow can be simply determined by dividing the actual urea clearance found, as calculated by the formula given earlier in this review, by the mean normal value at that flow.

For subjects differing markedly from the usual adult size Möller, McIntosh, and Van Slyke suggested the application of a correction factor so as to express urine flows per 1.73 square meters of body surface, that is, in terms of an average or standard man. This correction assumes that urea excretion varies directly as surface area. The data of Chasis and Smith, used to construct the aforementioned table of clearance values, have been corrected to this standard.

The new methods have also furnished data giving a clearer view concerning the behavior of phenolsulphonphthalein (phenol red) in the kidney. This dyestuff always gives clearances far above the inulin levels and reaches its highest values when the plasma concentration is 1 mg. per cent or less. In a recent study of renal clearances in forty-three normal men, Goldring Chasis, Ranges, and Smith (12) report a mean phenol red clearance of 391 cc. per minute (plasma concentration low), which is almost exactly three times the mean value of 130 cc. per minute found for inulin. Such values can only mean that the dye is being largely excreted (two-thirds) by the tubules at the same time that a minor fraction (one-third) is filtering through the glomeruli. The clinician should realize that in using this test he is employing a substance which measures a tubular activity much more than it evaluates a glomerular filtration rate. It will shortly be seen how a particular form of this test, made when plasma phenol red concentration is high, may measure a maximal rate of tubular excretory activity and so assess the active mass of renal tissue.

Inulin is now being used to study the behavior in the kidney of various drugs, vitamins, and hormones. Two examples of such use of this new tool may be mentioned. Taylor, Lowell, Adams, Spring, and Finland (32) have compared the clearances of sulfanilamide and sulfapyridine with the inulin values. These drugs have clearances between 20 and 50 cc., which are much lower than the glomerular filtration rates established by the inulin. It appears that two-thirds to three-fourths of these drugs must be reabsorbed in the tubules. This is a fact of outstanding clinical importance, since tubular absorption aids in maintaining the blood levels of these drugs. If sulfapyridine is given with glucose (intravenous injection), however, its clearances rise to 110 to 130 cc., or to the glomerular filtration level. It apparently forms a compound which is not reabsorbed by the tubules. Hence its blood level falls rapidly and treatment becomes relatively ineffective. Friedman, Sherry, and Ralli (10) have reported on the behavior of vitamin C. It is largely reabsorbed by the tubules at low plasma levels (0.03 to 2.05 mg. per cent), but its clearance is never zero. The values obtained lie in the range of 1 to 4 cc. per minute, that is, 3 per cent or less of the inulin clearance. The other 97 per cent is returned to the blood and conserved by the body.

Routine clinical procedures for the administration of inulin have been described by Alving and Miller (1), and by Findley and White (9). Alving and Miller use a single intravenous injection of 10 grams of inulin made up in 100 cc. of isotonic sodium chloride and given at a rate of 10 cc. per minute. One hour after injection the bladder is emptied and the urine discarded. Two consecutive hourly collections of urine are then made, accurately timed, measured, and analyzed for inulin. At the midpoint of each clearance period 15 cc. or more of blood are withdrawn by venipuncture. Plasma inulin is then determined and clearances are calculated by the usual formula. In this procedure, plasma inulin steadily declines and the slope of its curve of disappearance may be used as a measure of glomerular filtration rate. Findley and White advocate subcutaneous injections in the region of the axilla, and have secured consistent inulin and diodrast clearance values.

Alving and Miller (1), and several other of the authors previously cited, report on the inulin clearances in normal persons and in patients with renal disease. In glomerulonephritis clearances may fall to values as low as 5 to 10 cc., and the severity of the disease may be at least approximately assessed by this method. In infants and children, where collection of urine samples is difficult, Barnett (3) does not analyze the urine. He merely determines two or three points on the curve of plasma inulin, while it is declining after a single intravenous injection. The slope of the curve determined by these points permits a calculation of inulin clearance. He finds that clearances are reduced in the newborn but increase rapidly to higher levels after the fourteenth day of postnatal life.

MEASUREMENT OF RENAL PLASMA FLOW

A most interesting and valuable development of the clearance studies has come in the discovery that diodrast, an organic iodine compound opaque to roentgen rays and used in urological radiography, is so rapidly excreted by the tubule cells that at low plasma levels all of it may be eliminated in one passage of the blood through the kidney. It appears in the glomerular filtrate in the same concentration as in plasma, but much more of it passes out through the cells of the tubules. In their study of normal men, Goldring, Chasis, Ranges, and Smith (12) report a mean diodrast clearance of 688 cc., compared with the inulin mean of 130 cc.

The diodrast value signifies that at least this volume of plasma must have entered the kidney in each minute in order to deliver so much of the substance into the bladder urine. It does not enter the red cells, hence the clearances calculated give strictly plasma volumes. Diodrast is now being employed to measure renal plasma flow. The ratio of glomerular filtrate (inulin clearance) to renal plasma flow (diodrast clearance) gives the "filtration fraction." This fraction has a mean value of 18.9 per cent. In other words, about one-fifth of the blood plasma filters off as glomerular fluid with each passage of the blood through the kidney.

The effective whole blood flow may also be calculated from the data if the red cell percentages are known The mean value is calculated to be 1189 cc. per minute. Since cardiac outputs in adult humans range between 4000 and 5000 cc. per minute, it becomes evident that the two kidneys may receive as much as one-quarter of all the blood which leaves the heart.

Using the diodrast method, Chesley, Connell, Chesley, Katz, and Glissen (6) have recently studied renal plasma flow in eclampsia, preeclampsia and recurrent toxemia of pregnancy. They report normal flows, showing that renal ischemia is not a factor in these diseases. In chronic nephritis, however, they find renal blood flows to be considerably diminished. Smith, Goldring, Chasis, and Ranges (27) find renal blood flow to be diminished in hypertension at a time when the filtration rate is not affected. In such patients the filtration fraction is, of course, increased. Smith, Chasis, Goldring and Ranges (25) find the glomerular filtration rate in any one subject to be relatively independent of either ischemia induced by adrenalin, or hyperemia induced by typhoid vaccine or pyrogenic inulin. On the whole, it appears that in man and other mammals the glomerular filtration rate is relatively constant, even in some types of renal disease, and of rather limited value in diagnosis. In nephrosis, for example, inulin clearance may be normal. Renal blood flow measurements are more variable and of higher diagnostic value.

MEASUREMENT OF "TUBULAR EXCRETORY MASS"

In spite of a relative constancy in any one subject, it must be admitted that the data for glomerular filtration rates (inulin clearances) in groups of normal men and women are rather variable, and that acceptable normal standards are not yet in hand. Recently some investigators have corrected the raw data to "standard man" with a surface area of 1.73 square meters, on the assumption that kidney sizes will vary, at least approximately, in proportion to the surface area of the bodies. Even after this correction is applied, however, a considerable variability is observed in the data compiled by Goldring, Chasis, Ranges, and Smith (12). It would appear that no close correlation exists between the kidney size and surface area of the body.

A more promising approach to the attainment of standard values is furnished by the measurement of "tubular excretory mass" (T_m). This concept was introduced by the work of Shannon and Fisher (23), who demonstrated that in the dog the capacity of the tubule cells to reabsorb glucose reaches a certain maximal value as plasma glucose concentrations are raised, and that this value is not further increased even in extreme hyperglycemia. In similar manner Smith, Goldring, and Chasis (26) demonstrated in man that the absolute amount of diodrast excreted by the tubules reaches a maximum when the plasma level attains a value of about 25 mg. per cent. Further increases in plasma diodrast give no further rise in the amount excreted by the tubule cells. It is manifest that at these higher levels a tubular excretory mechanism is being presented with more material than it can immediately transport. These authors further show that if diodrast excretion by the tubules is maximal the clearance of phenol red is diminished, and vice versa, suggesting that both substances are excreted by a common tubular mechanism.

Smith and his colleagues argue that this maximal value is a measure of active renal tissue or tubular excretory mass. They express this value by the symbol T_m. Such a maximal value can be established for phenol red and hippuran as well as for diodrast. It is also now the custom to speak of glucose T_m, although here the symbol must be interpreted to mean "tubular absorptive mass." A definite glucose T_m in man has been established by these investigators. It is of interest to note that a similar phenomenon of maximal absorptive capacity was long ago noted by Cori (8) in the intestinal absorption of glucose. Even sodium chloride has been reported to show a similar maximal rate of intestinal absorption and does not behave as if it were merely diffusing out of the gut across the membranes. Very recently Harrison and Harrison (13) have discerned a maximal rate of phosphate reabsorption by the tubules of the dog's kidney.

The calculation of diodrast T_m values rests upon the simultaneous determination of inulin and diodrast clearances. Plasma diodrast must be raised to a value known to give the maximal tubular excretory rate. The amount of diodrast filtered per minute in the glomeruli can be calculated when the filtration rate (inulin clearance) and plasma diodrast concentration are known, since diodrast passes freely into the glomerular filtrate. The amount of diodrast arriving in the bladder urine per minute (UV) is determined by multiplying the minute volume of urine by the urinary diodrast concentration. This product exceeds the value of diodrast filtered in the glomeruli by the amount of the tubular excretion. The difference between the two or values is the diodrast T_m.

Measurements of diodrast T_m are now in progress in several laboratories. It has been found that this quantity in any one individual is more constant than the glomerular filtration rate. Its magnitude may be a direct measure of kidney size. Smith and his colleagues suggest its use to determine the residual active kidney tissue in renal disease. It is known to decline in some diseases long before the glomerular filtration rate is affected. It is probably of more diagnostic value than either glomerular filtration rate or renal plasma flow.

If the inulin clearance data of Goldring, Chasis, Ranges, and Smith (12) are corrected to a mean kidney size on the assumption that size is directly proportional to diodrast T_m, the values become much more consistent, most of them lying within a fairly narrow range of 120 to 160 cc. per minute. Such a correction of the raw data appears to the writer to be more valid than an adjustment of the values to standard man of definite surface area, but more extensive data must be at hand before final conclusions can be drawn.

CLINICAL EVALUATION

These new technics for the measurement of glomerular filtration rate, renal plasma flow and maximal excretory or absorptive capacity, furnish tools by which renal function can be analyzed in detail. The technics are somewhat more difficult than those which are now routinely employed in clinical laboratories. It may be found that widespread use of these methods in hospital diagnosis is not practicable. A few well-equipped clinical laboratories will have to take the lead in exploring the practical possibilities. In any case, it is now possible in research work to study the behavior in the kidney of drugs, vitamins, and hormones with a delicacy and accuracy never attained before. Valuable information is coming in by which various clinical procedures may be corrected or improved.

A basic desideratum in this field are normal standards to which pathological variations may be referred and by which the severity of disease may be assessed. It appears at the moment that these normal standards must be built around measurements of kidney size. Conceivably, the size might be determined by radiography, but it appears more immediately practicable to measure the magnitude of some tubular function, either absorptive or excretory, when operating at its maximum. Diodrast T_m now appears to be the leading contender for this honor.

When this basic point has been decided the values found for glomerular filtration rate and renal plasma flow will have to be related to the kidney size. Corrected data may take the form of "glomerular filtration (inulin clearance) per unit of diodrast T_m per minute" and "renal plasma flow (diodrast clearance) per unit of diodrast T_m per minute" (25). If such direct correlations are established it seems useless to correct the data further for body surface area, since convincing information that kidney size is a function of that area is not available.

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CONSERVATIVE TREATMENT OF NEPHROPTOSIS*†

A New Technique

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Nephroptosis or movable kidney is the term applied when the excursions of the organ exceed the normal movements incident to respiration and change of posture. The normal kidney is loosely fixed by the vascular pedicle, fatty capsule, perirenal fascia, and intra-abdominal pressure. It moves, with respiration, up to 5 cm. and often varies in the upright position with no impairment of function.

A palpable kidney is not necessarily pathologic nor is abnormal movability unless it impairs free urinary drainage or affects the renal blood or nerve supply. Without symptoms resulting from these impairments the condition is of little clinical importance and requires no treatment.

The first reference to the condition was that of Meuse in 1495. The first suspension was performed by Hahn in 1881. This procedure gradually became too frequently employed over a thirty year period owing to overenthusiasm. It was followed by a period of discredit that to some extent still persists. With the steady advance in diagnosis of nephric disease in recent years there has resulted the belief that nephropexy is a satisfactory operation in carefully selected cases.

The etiologic factors involved are both congenital and acquired. The anatomic deficiency in which the renal fossae are abnormally small but dilated at the inferior portion is almost constantly found. This probably accounts for the greater prevalence of the condition in women. The perirenal fascia that is well adapted for the support of quadrupeds apparently loses its strength and is frequently defective in the upright position. With the loss of perirenal fat the weight is placed upon the trabeculae, which stretch and allow a change in position. Other factors that may contribute are pregnancy, trauma or occupational conditions that cause long-continued jolting, standing or bending.

Since this paper deals with the presentation of a method of treatment, no attempt is made to discuss the pathology or symptomatology of the condition. However, it is important to mention some of the more essential diagnostic procedures, for unless all due stress is laid here surgery will not be considered where indicated, there will be an unwise selection of operative cases, unsatisfactory surgical procedure, and, most important,

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an unhappy patient. A proper diagnostic procedure must be followed and a corrective method then correctly applied.

First, the degree of abnormal motility should be established and the presence of hydronephrosis and infection then determined. The possibility of aberrant vessels, fibrous bands, kinks, strictures, unusual ureteral insertion and periureteritis also must be considered. After this is completed, it is necessary to decide whether the treatment should be palliative or surgical. The degree of mobility, hydronephrosis, pelvic and ureteral distortions can all be determined by means of retrograde pyelography, using the Trendelenburg and erect positions. Excretory pyelograms are unsatisfactory. The determination of the presence of infection is important. Reduplication of pain symptoms can be accomplished by injection and is important in differential diagnosis when the condition is coexistent with other pathology. Emptying time may be definitely established.

Conservative treatment first should be tried in all but the most pronounced cases of renal mobility. Nonsurgical treatment for several months is advisable. This consists of abdominal support, exercise, dietary measures, bed rest, ureteral dilatation where indicated, and chemotherapy if infected, all followed by a carefully fitted abdominal belt. When conservative measures have failed to relieve the symptoms, where abnormalities interfere with drainage and function, or where the condition is progressive despite these methods, surgical fixation is indicated.

It is important to remember here that nephroptosis associated with visceroptosis is usually bilateral and an operation is likely to increase rather than alleviate the symptoms.

Once the selection of the case is made a satisfactory type of operation, properly performed, may follow. Simple fixation is not sufficient. Ureterolysis, ureteropyeloplasty, lysis of aberrant vessels, and sympathectomy are often indicated. When these have been dealt with an applicable fixation may be done. The word applicable is used advisedly because a vast number of procedures are not adaptable to all conditions. Quite frequently they appear more satisfactory when viewed through the artist's eye than when the surgeon attempts to apply them to always differing conditions. Here, as in many operations, the method must be fitted to the patient rather than to apply a fixed method to varying lesions. Another fault with many procedures is the unnecessarily complicated method advised; simplicity in surgery is a virtue that needs no extolling.

A method is here presented that seems to meet all requirements. It is perhaps not entirely original, but it has been applied to a number of cases to date, with good results in adults and children, both male and female.

Method of Procedure. Before the incision is made it is essential that the ribs be counted from above downward. In the absence of a twelfth rib the pleura may be injured. In the event of a thirteenth the exposure may be insufficient for complete and essential delivery of the kidney; furthermore, the intercostal muscle between the eleventh and twelfth ribs is important in this method.

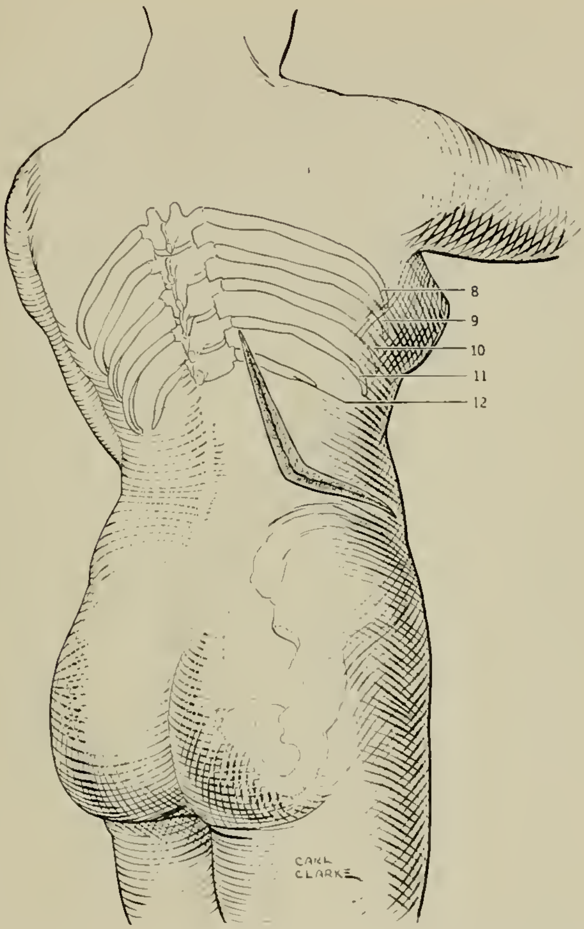

Fig. 1. A modified hockey stick incision. The intercostal muscle is exposed in the upper end of the wound. An adequate exposure is obtained with a maximum of consideration to anatomic details.

The incision used, as illustrated in Figure 1, differs from the hockey stick incision of Mayo, which is a posterolateral one, in that the superior portion begins from a point on the level of the inferior border of the eleventh rib, approximately one and one-half inches from the spinous process, downward parallel but lateral to the erector spinae to within approximately an inch of the iliac crest, thence forward nearly parallel to the crest. The external and internal oblique are cut as presented. The anterior border of the latissimus dorsi is cut as necessary. The first lumbar nerve and its branches usually lie on the border of the quadratus lumborum and are easily protected. The twelfth intercostal nerve parallels the anterior border of the incision but must be protected when exposing the twelfth rib. The exposed perirenal fat is opened as far posteriorly as possible and the kidney is mobilized. The ureteropelvic junction and upper portion

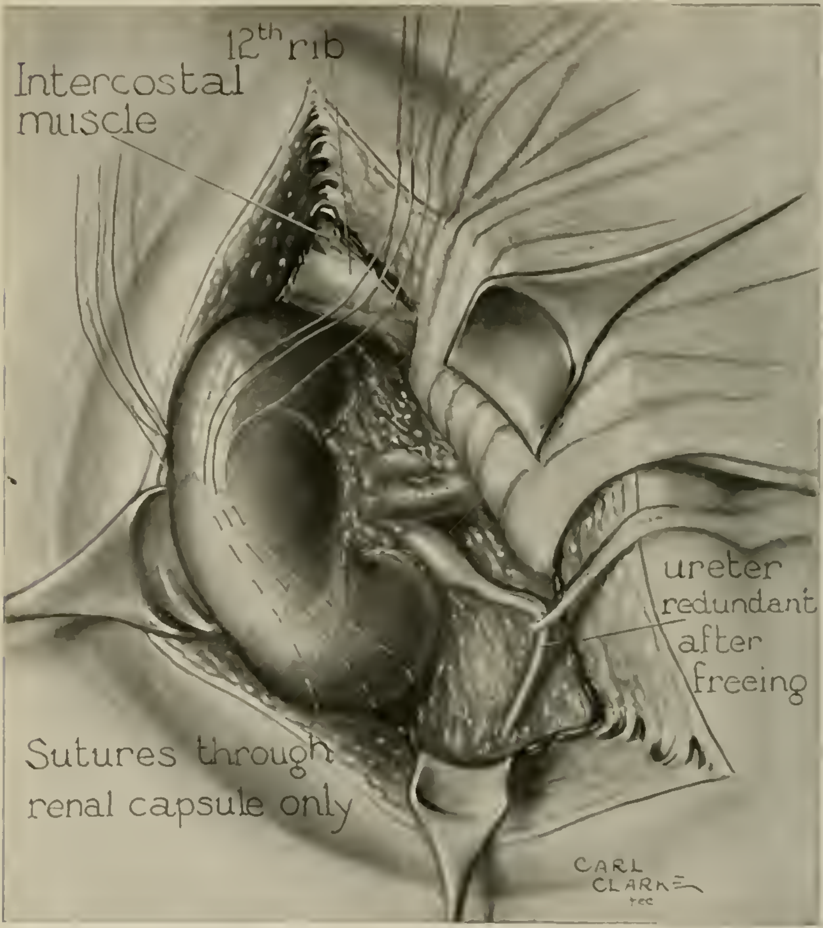
12th rib
Intercostal muscle
ureter redundant after freeing
Sutures through renal capsule only
CARL CLARKE fec

FIG. 2. A method of placing sutures in the renal capsule. These sutures may vary in position as desired. The pedicle and ureter are freed of connective tissue. The anterior surface of the kidney is shown and the ureter is pulled medially.

of the ureter must then be freed of all constricting bands and aberrant vessels. Care is taken to avoid injury to the fibrous renal capsule.

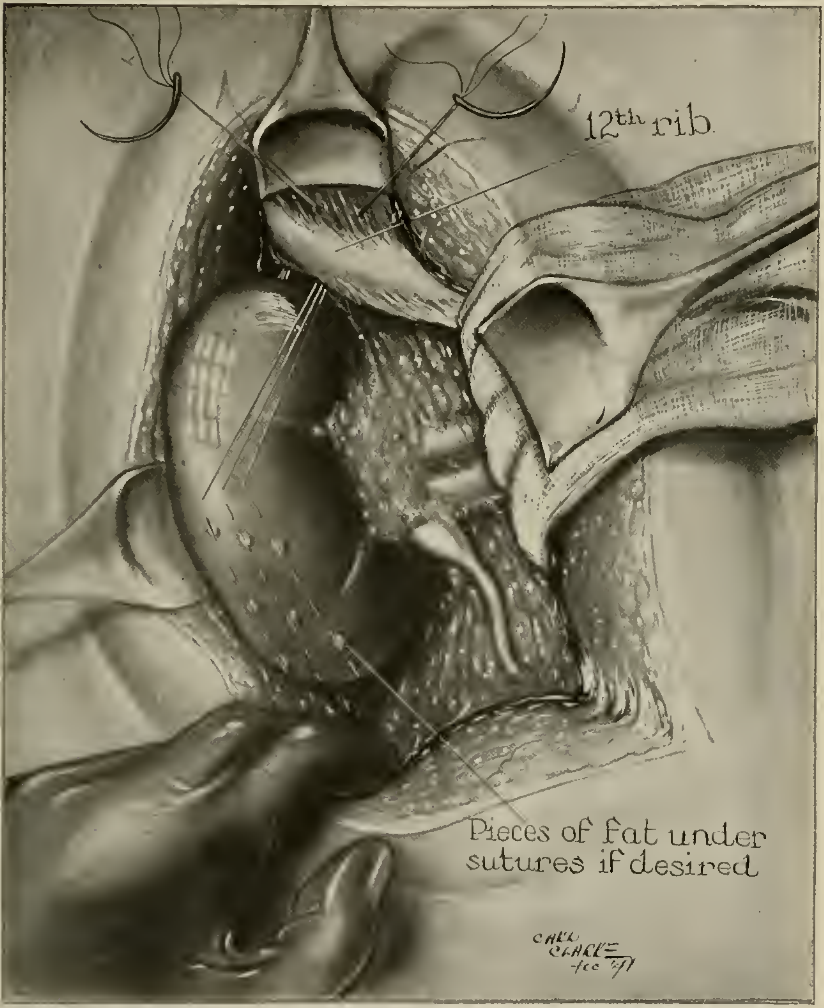

Fig. 3. The free ends of the capsular sutures are brought out through the intercostal muscle above the twelfth rib before the kidney is drawn into place.

In this technique three atraumatic chromic catgut sutures on straight needles are used. If preferred, narrow ribbon gut will serve the same purpose. Before proceeding, the kidney is replaced in the wound in the position which seems most desirable. Note is made as to the level directly underlying the intercostal space. The organ is again delivered and at the point above determined, usually at the juncture of the middle and lower third of the kidney, but varying as desired, and about three-quarters of an inch lateral to the greater curvature the sutures are placed in purse-string fashion, as shown in Figure 2, in the capsule only. If desired, small bits of

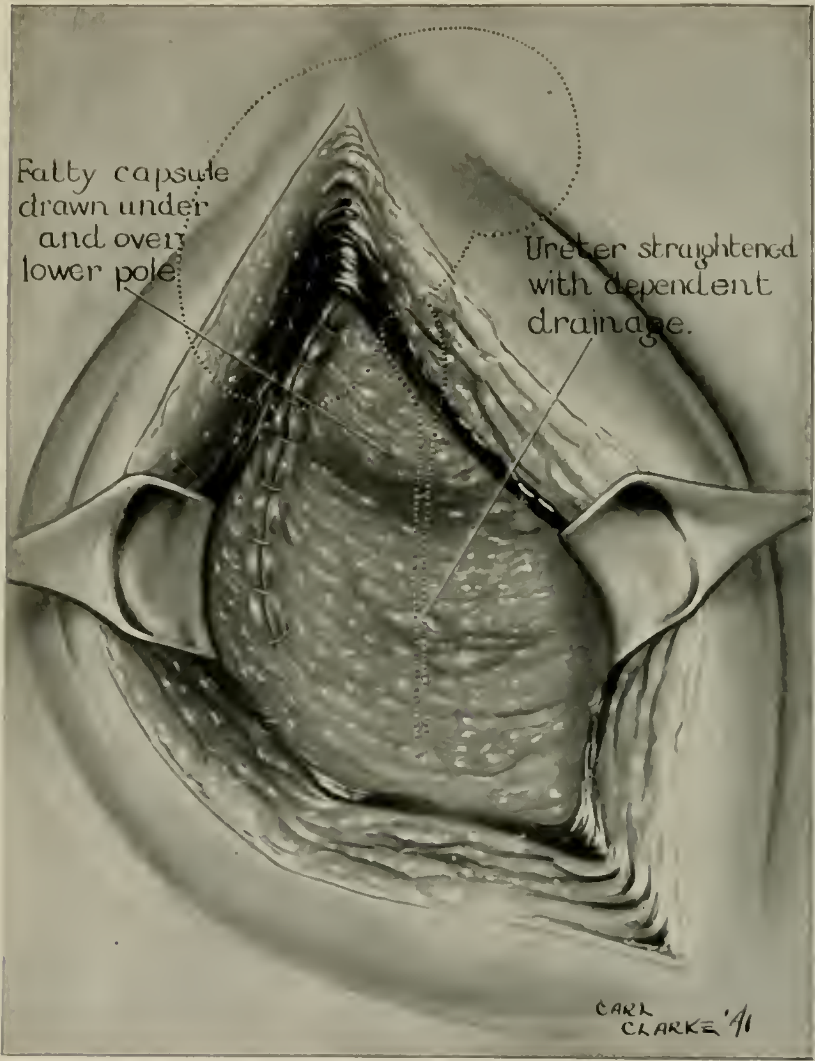
Fatty capsule drawn under and over lower pole
Ureter straightened with dependent drainage.
CARL CLARKE '41

FIG. 4. An illustration of the kidney in the desired position. Overcorrection and dependent drainage are obtained. The fatty capsule supplies secondary support.

fat may be placed under the sutures at the exposed intervals. These three sutures may be placed eccentrically, as seems indicated for the best position. The free ends on either side are placed on two medium-sized curved non-cutting needles. When it is definitely certain that the pleura does not extend abnormally low, the needles are passed out through the intercostal muscle close to the upper border of the twelfth rib about three-fourths of an inch apart, as in Figure 3. Traction raises the kidney into place before the sutures are tied. At this point it will be noted that the axis has been changed, the lower pole is drawn upward and outward, thus providing

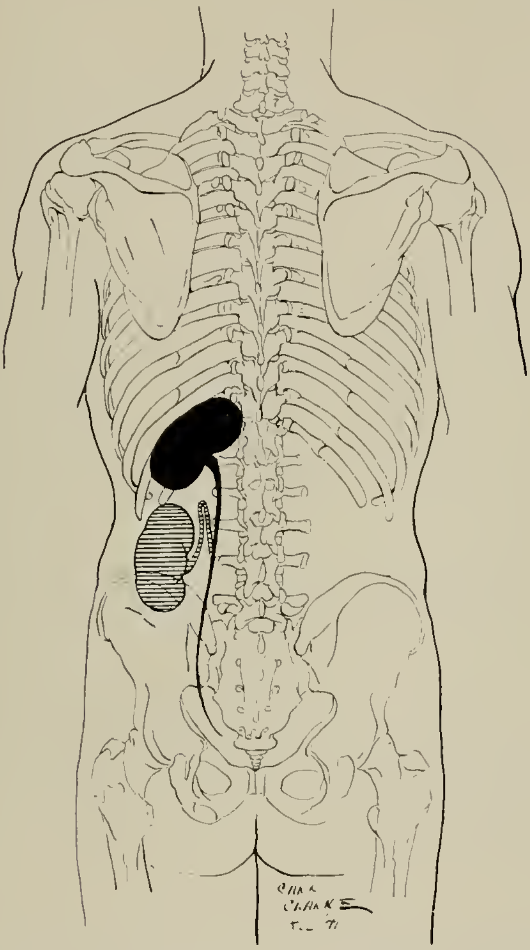

FIG. 5. A diagrammatic posterior view of a hypothetical case and the degree of correction possible.

dependent drainage, kinks and tortuosities have been removed, and the ureter straightened. The organ will then lie snugly in its new bed against the ribs and diaphragm laterally and superiorly, and the peritoneum medially. Since the adrenal gland does not descend with ptosis it is affected in no way. Decapsulation seems superfluous for apparently the kidney rapidly becomes adherent in its new position. If desired, the perirenal fat may be drawn under and over the kidney, as illustrated in Figure 4, and attached to the border of the quadratus lumborum. Postoperatively the patient should be kept in the recumbent position, either flat or with the foot of the bed slightly elevated, for at least twelve days to allow supporting adhesions to form.

SUMMARY

Stress has been placed on the importance of selecting cases by the adequate use of modern urologic procedure. Conservative treatment is usually indicated before surgical procedure. The operative method should insure complete freedom from obstructive lesions as well as correction of position. The technique here presented offers an incision demonstrating important anatomic detail with a minimum of operative damage. The method of fixation is extremely simple, eliminates decapsulation, and has proved satisfactory.

The author wishes to express his sincere gratitude to Dr. Herbert H. Howard of Boston City Hospital, on whose service this procedure was developed.

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VULVOVAGINITIS IN CHILDREN*†

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The rationale of estrogens in the treatment of specific vulvovaginitis has been well established. However, in addition to the many natural estrogenic products on the market, the relatively recent acquisition of two new drugs—sulfanilamide and stilbestrol—has somewhat confused the situation. The following series of 226 cases of vulvovaginitis which were satisfactorily treated and followed is presented in an effort to clear up some of this confusion.

Each case was studied for a minimum of three months after the first negative smear, this time being the arbitrarily established criterion for a cure. The return of a positive smear in less than three months is classified as a recurrence, in more than three months as a reinfection. Approximately 60 per cent of the cases were followed for one year, the remainder for varying periods of from three to eleven months. In this series were 198 colored patients and twenty-eight white. There was a history of contact with an infected person in fifty-nine cases. Positive contacts were always sought, frequently without success, and when they were located an attempt was made to remove the patients to new surroundings. It is interesting to note here that in a few cases exhibiting repeated reinfections for whom no contact could be ascertained, a permanent cure was readily affected after moving the patients to a new neighborhood. There are fifteen known cases of reinfection in this series, all in colored patients, from varying periods of five months to three years after treatment.

Diagnosis was made in the presence of clinical signs and symptoms and a positive smear for gonococci. Treatment was not instituted until a definitely positive smear was obtained. The methods of treatment employed were oral administration, local insufflation, and vaginal suppository. No patients were treated by intramuscular injection or by inunction. Each method of treatment is discussed separately.

All hydrogen ion concentration (pH) determinations were made with nitrazine paper. There were no vaginal cultures made. A complete physical examination, including rectal, was always carried out before and after treatment.

CHEMICAL AGENTS

1. Five patients were given a biweekly vaginal insufflation of washed sand and kaolin. This was done in an attempt to cure the disease by

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thickening the vaginal mucosa purely from mechanical irritation in an alkaline medium. Vaginal biopsies from patients treated with floraquin (Fig. 2) suggested that mechanical irritation, aside from a change in pH, might be a definite factor in thickening the mucosa. That there were two cures in the five cases so treated, both of which remained well for over one year, is suggestive even if inconclusive.

TABLE 1

Results of Sand and Kaolin Therapy

DURATION OF TREATMENT	NO. OF CASES	RESULTS
5 weeks	4	1 cure, 3 failures
6 weeks	1	1 cure

TABLE 2

Results of Floraquin Insufflation

DURATION OF TREATMENT	NO. OF CASES	RESULTS
5 weeks	12	2 cures, 10 failures

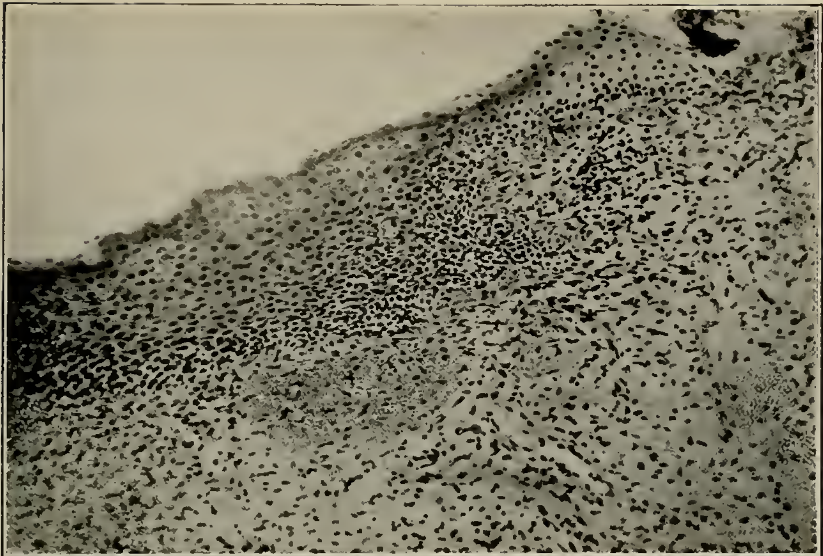
TABLE 3

Results of Treatment by Floraquin Suppository

DOSAGE	DURATION OF TREATMENT	NO. OF CASES	RESULTS
	weeks		
Twice daily	4	1	1 cure
Twice daily	5	6	5 cures, 1 failure
Three times daily	4	1	1 cure
Three times daily	5	22*	16 cures, 5 failures, 1 recurrence

* Two of these patients were treated in an intermittent manner because of a lack of co-operation on their part. Such cases are included throughout this report because the end results of therapy were satisfactory. They are not, however, included in any statistical conclusions and the number of them represented in any table will be indicated.

2. Floraquin vaginal insufflation was administered biweekly to twelve cases. In none of these was there a history of any previous specific treatment. Each of the two cures had a negative smear at the end of four weeks of treatment. The failures all had positive smears at the end of five weeks of treatment. Pure epithelium (type IV vaginal reaction as noted in wet preparation or washing) was not attained in any of the twelve cases. A pH of 4.5 was obtained in two cases, and Döderlein's bacilli were noted in three cases during treatment. There were no complications of either the disease or the treatment.



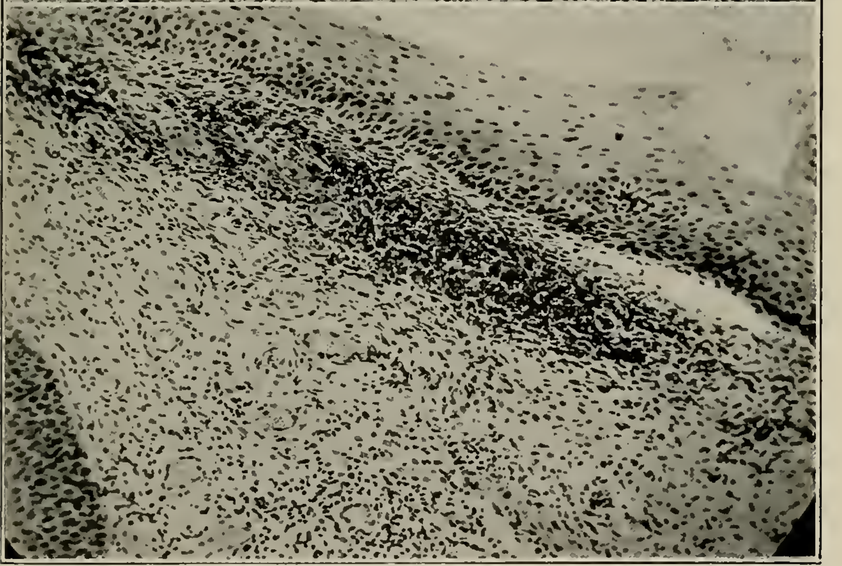


FIG. 1. Vaginal biopsy taken from patient treated with sand and kaolin. The thickening of the vaginal mucosa with submucosal inflammatory reaction is still present as compared to the thick mucosa and healthy submucosa of patients treated with estrogenic substances as shown in Fig. 3d.

FIG. 2. Biopsy taken after five weeks of floraquin treatment, showing a marked subepithelial inflammatory reaction despite a negative smear after the fourteenth day. This is a typical biopsy after floraquin treatment.

3. Floraquin vaginal suppositories were used in thirty cases, none of which had received any previous specific therapy. All the failures and the one recurrence with floraquin therapy were subsequently cured either by estrogenic treatment or by stilbestrol.

TABLE 4

Results of Sulfanilamide Therapy

TOTAL DOSE (GRAINS)	DAYS TREATED	AGE	REACTIONS	RESULTS
630	35	4	None	Failure
595	56	2	None	Failure
1,060 supplemented with 50% sulfanilamide suppository daily for 14 days	30	10	None	Failure
420 supplemented with 50% sulfanilamide suppository daily for 7 days	21	3	Marked dyspnea	Failure
1,450 supplemented with 50% sulfanilamide suppository daily for 7 days	42	8	None	Failure

TABLE 5

Results of Treatment by Amniotin Perles

TOTAL DOSE i.u.	DAYS TREATED	NO. OF CASES	RESULTS
14,000	14	3	3 cures
32,000	32	1	1 cure
35,000	35	70	69 cures, 1 recurrence
40,000	40	2	2 cures
42,000	42	1	1 cure
49,000	49	1	1 cure
56,000	56	1	1 failure
158,000*	158	1	1 cure
Intermittent Treatment			
31,000	52	1	1 cure
35,000	42	3	3 cures
42,000	49	1	1 cure
43,000	63	1	1 cure
45,000	56	1	1 cure

* This large dose was administered entirely by mistake.

Complications of the disease: One patient had arthritis of the knee. The vaginitis failed to respond to floraquin but was cured by estriol. The arthritis responded to bed rest.

Complications of the treatment: In one case local irritation resulted from floraquin. This subsided when treatment was stopped.

The earliest negative smear was obtained in seven days, the average in twenty-four days. Four cases never showed a negative smear. One case had a negative smear after three weeks but was positive again at the end of the treatment. Pure epithelium (in wet vaginal preparations) was developed in only four cases, the earliest of which was at the end of seven days; the average case required nineteen days. A pH of 4.5 was present in six cases, and Döderlein's bacilli were found in thirteen cases during treatment. It is interesting to note that two smears showed both Döderlein's bacilli and gonococci at a pH of 4.5, and another smear showed Döderlein's bacilli present at a pH of 7.0.

4. Five patients were treated primarily with sulfanilamide, all entirely without success.

ESTROGENS

1. Amniotin perles, each containing 1000 i.u., were administered vaginally in eighty-seven cases, eleven of which had had some previous trial of specific treatment without success.

Complications of the disease: One patient had swelling of the lumbar spine which subsided with hospitalization. A definite diagnosis of the spinal condition was never made.

Complications of the treatment: Thirteen patients exhibited slight to moderate bilateral breast hypertrophy, all of which subsided with cessation of treatment. One patient developed masturbation and perversion, which also subsided with cessation of treatment.

The single recurrence (two months following treatment with 35,000 i.u.) had a second similar course, with a cure resulting. The one failure (after 56,000 consecutive i.u.) was cured by employing supplementary stilbestrol orally. One case had a negative smear at the end of treatment, but a discharge persisted. This was checked by a floraquin vaginal suppository employed three times daily.

The earliest negative smear was developed in seven days, the average being twenty-six days. The earliest pure epithelium was produced in fourteen days, the average in twenty-seven days. A pH of 4.5 was obtained in thirty-five cases, and Döderlein's bacilli were present in eighteen cases during treatment. One smear showed Döderlein's bacilli and gonococci both present at a pH of 4.5.

Comment: In the cases receiving less than thirty-five nightly treatments therapy was stopped because of the unusual rapidity of response, namely, a negative smear and type IV vaginal wet preparations of pure epithelium. On the other hand, a few cases appeared resistant to estrogenic therapy locally and necessitated longer periods of treatment and on one occasion supplementary treatment, that is, oral stilbestrol. The one case in which

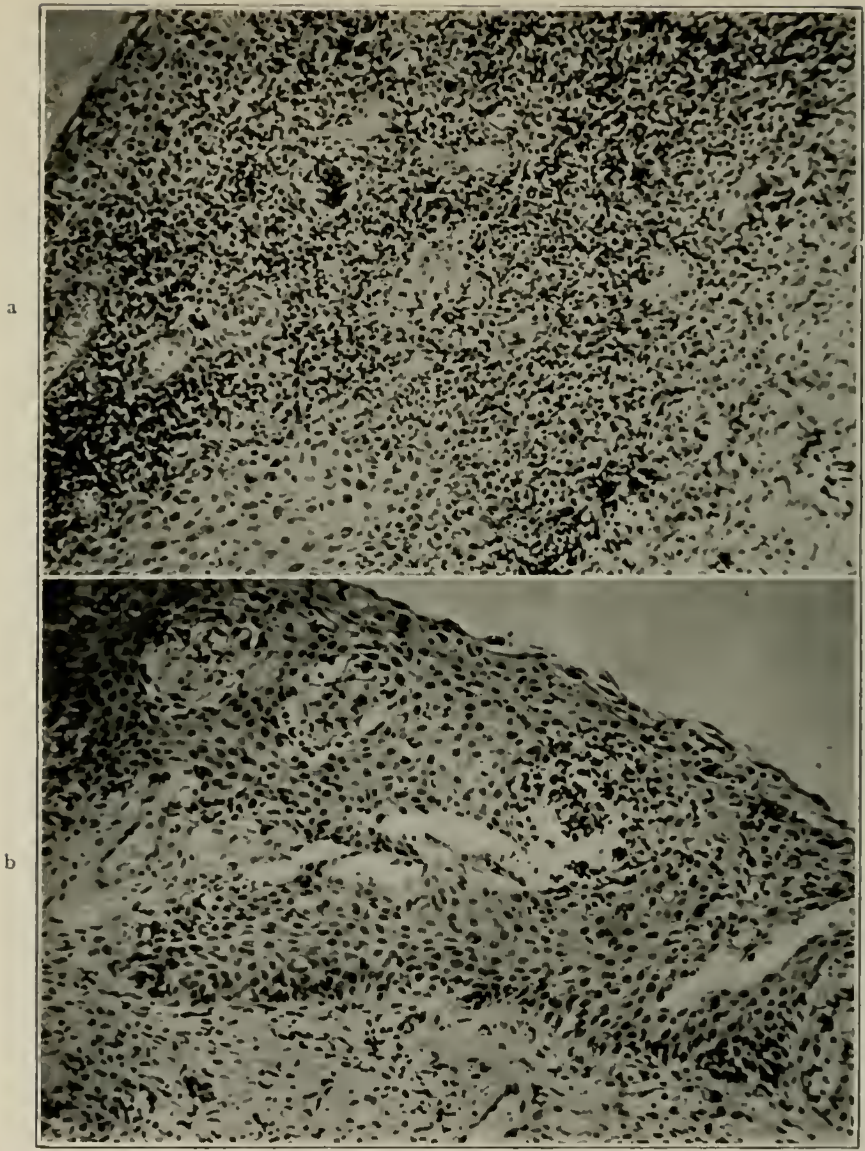


FIG. 3. Successive biopsies of the vaginal mucosa during and after treatment with amniotin perles.

a, Before treatment. b, After two weeks of treatment.

treatment was markedly prolonged by error (158,000 i.u.) without any untoward reactions indicates the relative harmlessness of this type of treatment.

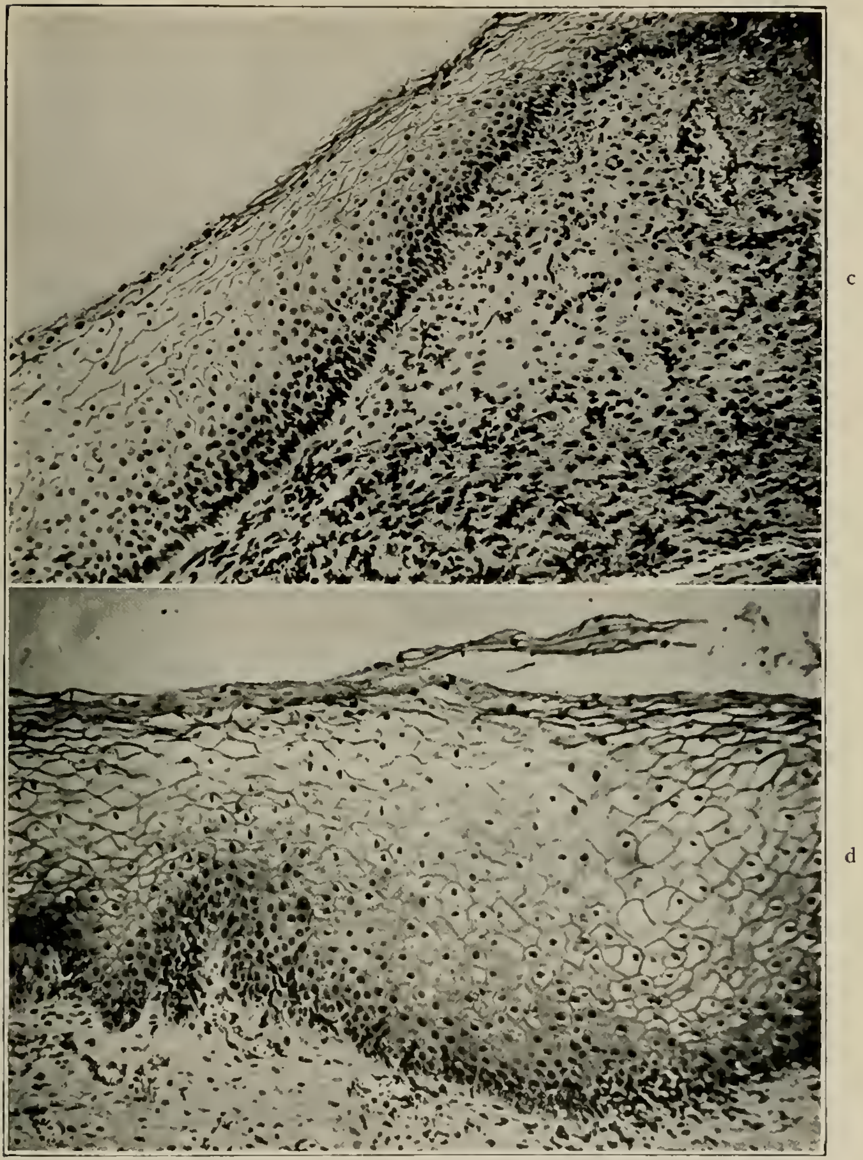


Fig. 3c. The same mucosa as seen in Figures 3a and b, after five weeks of treatment.
d. Two weeks after cessation of treatment, showing maximal thickening of epithelium owing to cumulative action of the drug.

2. Estriol gelatin capsules in the vagina were used in twenty-four cases, six of which had been treated previously by other methods with failure. There were no recurrences and no failures.

Complications of the disease: One case had condylomata accuminata, which cleared up with the treatment of the vaginitis.

Complications of the treatment: Two patients developed slight bilateral breast hypertrophy, which cleared up with cessation of the treatment.

The earliest negative smear was obtained in seven days, the average in nineteen days. The earliest development of pure epithelium took place in seven days, the average developed in twenty-three days. A pH of 4.5 was reached in nineteen cases, and Döderlein's bacilli were present in twelve cases during treatment.

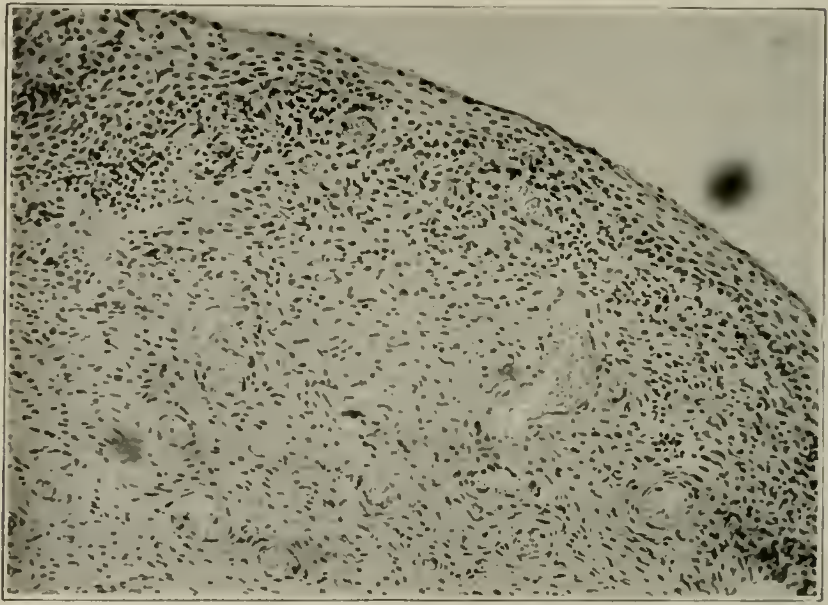


Fig. 3e. The same mucosa seen in Figures 3a. b, c, and d, four weeks after cessation of treatment.

3. Reed and Carnrick oral estrogenic tablets (1000 i.u. each) were administered by the vaginal route in eighteen cases, none of which had had any previous attempt at therapy. The one recurrence was treated again with a similar course of 35,000 i.u. and cured.

Complications of the disease: Two patients had urethritis, one being present at the onset, in the other developing with recurrence of the vaginitis. Both cleared up with the use of concomitant sulfanilamide. One patient developed a right-sided inguinal adenitis which suppurated and necessitated surgical drainage. This condition was greatly improved with the oral use of sulfanilamide and eventually healed completely.

Complications of the treatment: Fourteen patients exhibited slight bilateral breast hypertrophy, all of which cleared up with cessation of treatment. One patient (age six) had a persistent slight bilateral breast hypertrophy after five months. Another developed marked bilateral breast hypertrophy and slight lower abdominal pain with the treatment. The pain stopped promptly on cessation of treatment and the breast hypertrophy resolved. The earliest negative smear was produced in seven days, the average in twenty-eight days. The earliest development of pure epithelium occurred in seven days, the average required twenty-eight days. A pH of 4.5 was attained in eleven cases, and Döderlein's bacilli were present in eleven cases during treatment.

TABLE 6

Results of Treatment with Estriol Capsules

DOSE	NO. OF CASES	RESULTS
.03 mg. capsule every night for 35 days	20	20 cures
.06 mg. capsule every night for 35 days	4	4 cures

TABLE 7

Results of Therapy with Reed and Carnrick Tablets

TOTAL DOSE	DAYS OF TREATMENT	NO. OF CASES	RESULTS
i.u.			
35,000	35	14	13 cures, 1 recurrence
42,000	42	1	1 cure
45,000	45	1	1 cure
49,000	49	2	2 cures

Comment: Treatment with amniotin perles, estriol capsules, and estrogenic tablets was always possible without injuring the hymen and with a minimum of discomfort to the patient.

STILBESTROL

1. Six patients were treated by stilbestrol vaginal suppository. The one recurrence was cured by the oral use of stilbestrol. There were no complitions of the disease.

Complications of the treatment: Slight bilateral breast hypertrophy was noted in two cases, marked hypertrophy in one case. All cleared up with cessation of treatment.

The earliest negative smear was obtained in twenty-one days, the average in thirty-five days. The earliest development of pure epithelium took place in twenty-one days, the average required twenty-nine days. A pH of 4.5 was attained in three cases, and Döderlein's bacilli were not found in any cases during treatment.

TABLE 8

Results of Treatment by Stilbestrol Suppository

DOSE	DAYS TREATED	NO. OF CASES	RESULTS
0.1 mg. suppository every night	21	1	1 cure
0.1 mg. suppository every night	35	2	2 cures
0.1 mg. suppository every night	42	2	1 cure, 1 recurrence
0.1 mg. suppository every night	49	1	1 cure

TABLE 9

Results of the Use of 1.0 mg. Three Times Daily

TOTAL DOSE	NO. OF DAYS TREATED	NO. OF CASES	RESULTS
mg.			
21	7	2	2 cures
24	8	1	1 cure
42	14	5	5 cures
51	17	1	1 cure
	Intermittent Treatment		
47	26	1	1 cure
63	28	1	1 recurrence
66	38	1	1 cure
84	35	1	1 cure
84	42	1	1 cure
84	70	1	1 cure

TABLE 10

Results of 1.0 mg. Daily Dosage

TOTAL DOSE	NO. OF DAYS TREATED	NO. OF CASES	RESULTS
mg.			
7	7	1	1 cure
14	14	12	10 cures, 2 recurrences
18	18	1	1 recurrence
21	21	2	2 cures
28	28	1	1 cure
35	35	1	1 cure
49	49	1	1 cure

2. Oral stilbestrol was given in doses of 1.0 mg. three times daily in fifteen cases. The one recurrence was cured by an additional dose of 1.0 mg. daily for fourteen days.

Complications of the disease: One patient had arthritis of the mediotarsal joint, another had arthritis of the knee, elbow, and ankle. Both cleared up with bed rest and treatment of the vaginitis.

Complications of the treatment: There was slight to moderate bilateral breast hypertrophy in ten cases and marked hypertrophy in three cases. Six patients developed hypertrophy of the external genitalia. Interestingly enough, all six of these had hypertrophy of the clitoris. These complications all subsided with cessation of the drug. One patient (age eleven but not in puberty) menstruated for one day after the drug was stopped. There were no toxic reactions in any case.

TABLE 11

Results of Supplementary Sulfanilamide Therapy

COMPLICATION	TOTAL DOSE	AGE	NO. OF DAYS TREATED	RESULTS
	grains			
Urethritis	280	2	14	Cure
Urethritis	200	3	16	Cure
Inguinal adenitis	240	11	3	Marked improvement
Salpingitis	270	5	3	Cure

TABLE 12

Summary of Efficacy of the Various Types of Treatment

TYPE OF TREATMENT	NO. OF CASES	FAILURE AND RECURRENCE	DEVELOPING SECONDARY SEX CHARACTERISTICS
		per cent	*per cent*
Sand and kaolin insufflation	5	60	0
Floraquin insufflation	12	83	0
Floraquin suppository	28	26	0
Sulfanilamide	5	100	0
Amniotin suppository	80	2.5	17
Estriol capsules	24	0	9
Reed and Carnrick estrogen tablets	18	5.5	83
Stilbestrol suppository	6	15	50
Stilbestrol (oral) 1 mg. t.i.d.	9	0	90
Stilbestrol (oral) 1 mg. daily	19	15	82

The earliest negative smear was obtained in seven days, the average in nineteen days. The earliest development of pure epithelium took place in seven days, the average required twelve days. A pH of 4.5 was attained in seven cases, and Döderlein's bacilli were observed in two cases during treatment.

3. An oral daily dosage of 1.0 mg. was employed in nineteen cases. There

were three recurrences. One of these was treated for fourteen days and recurred one month later. This patient was given fourteen more days of treatment with 1.0 mg. daily and cured. Another patient was treated for fourteen days and had a recurrence in two weeks. She was treated similarly again but there was a second recurrence which finally was cured by the use of Reed and Carnrick estrogenic tablets. The third patient was treated for eighteen days and had a recurrence in two months. An additional seven days of treatment with 1.0 mg. daily resulted in a cure.

Complications of the disease: One case had condylomata accuminata which improved with treatment of the vaginitis. Another had salpingitis which subsided with supplementary sulfanilamide.

Complications of the treatment: Slight bilateral breast hypertrophy was noted in fifteen cases and marked hypertrophy in two cases. There was hypertrophy of the external genitalia in four cases. All cleared up with cessation of the treatment, except one patient (age nine) who has had persistence of slight bilateral breast hypertrophy and pubic hair for twelve months. One patient developed nausea with the treatment. There were no other toxic symptoms.

The earliest negative smear was obtained after six days, the average after fourteen days. The earliest development of pure epithelium was noted in six days, the average development required fourteen days. A pH of 4.5 was attained in fourteen cases, and Döderlein's bacilli were noted in six cases during treatment.

4. An oral dose of 0.1 mg. three times daily was employed in one case. This patient was treated for fourteen days and cured. Slight bilateral breast hypertrophy was noted at the end of treatment. This promptly subsided. There were no toxic symptoms.

5. An oral daily dose of 0.1 mg. was given to three patients. One, treated for twenty-eight days, was cured. The other two were treated for thirty-five days; one was cured and the second recurred. The recurrence was cured by a dosage of 1.0 mg. daily for fourteen days. Two of these three cases developed slight bilateral breast hypertrophy which subsided with cessation of treatment. There were no toxic symptoms.

TREATMENT OF COMPLICATIONS

Four patients had complications which necessitated treatment with supplementary sulfanilamide. Three were treated for the vaginitis with Reed and Carnrick estrogenic tablets and one with stilbestrol. Other complications that were not treated with sulfanilamide consisted of two cases of condylomata accuminata and four cases of arthritis. The condylomata subsided with the treatment of the vaginitis. The cases of arthritis responded to bed rest and treatment of the vaginitis. The knee joint was involved in one, the lumbar spine in the second, the mediotarsal joint in the third, and the knee, elbow and ankle in the fourth.

CONCLUSIONS

These studies indicate that estrogenic substance, in any form, administered vaginally is the most effective therapeutic agent for the treatment of gonococcal vaginitis in children. The treatment should be of sufficient strength and administered over a long enough period of time to convert the infantile mucosa into the adult type as evidenced by a type IV vaginal smear. The average daily dose of estrogenic substance that meets these requirements is 1000 international units, or its equivalent. Smaller doses may be satisfactory, larger ones are usually unnecessary. The average duration of such treatment is thirty-five days, although longer periods may be needed in resistant cases.

Sulfanilamide is of little value in the treatment of the vaginitis. This has been shown to some extent in this study and has been well brought out by other workers. However, it is an effective drug when used for the treatment of some of the complications of the disease in conjunction with estrogenic therapy.

Oral stilbestrol is an effective therapeutic agent in this condition. Its use has not given rise to toxic signs or symptoms. These qualities are offset by the high incidence of the development of secondary sex characteristics associated with its use. This result is comparable to that produced by intramuscular injection of estrogens. Because of this characteristic it is recommended that this potent drug be reserved for supplementary therapy in those cases resistant to vaginal estrogen treatment.

The authors wish to express appreciation to the Robert Garrett Hospital for Children for some of the cases used in this series, and to extend sincere thanks to the following companies for their cooperation and the materials used in this study: E. R. Squibb & Sons, Eli Lilly and Co., G. D. Searle & Co., Abbott Laboratories, Parke Davis & Co., and Reed and Carnrick.

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POLLEN COUNTS*†‡

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In July, 1938 the first of an annual series of pollen counts for the Baltimore area were published (1). The results for subsequent years have been published annually since then (2, 3).

It is desired to call attention to an error that occurred in the graph published in April, 1940; it should have been for 1939 but was erroneously dated 1940. The period covered by the present report is for the latter year.

COMMENT

The season again varied somewhat from the usual in that the pollen counts for the latter half of August were extremely low. Suddenly, on Labor Day they jumped tremendously and continued at a high level for a short period. This was clinically important because all of the patients treated were convinced, during the last part of August, that the treatment was extraordinarily effectual whereas their complete lack of symptoms simply paralleled the small amount of pollen in the air.

METHOD

The method used was that given in detail in 1939 (2) and will not be repeated here.

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‡ Pollen counts supervised by Selma Rosenberg.

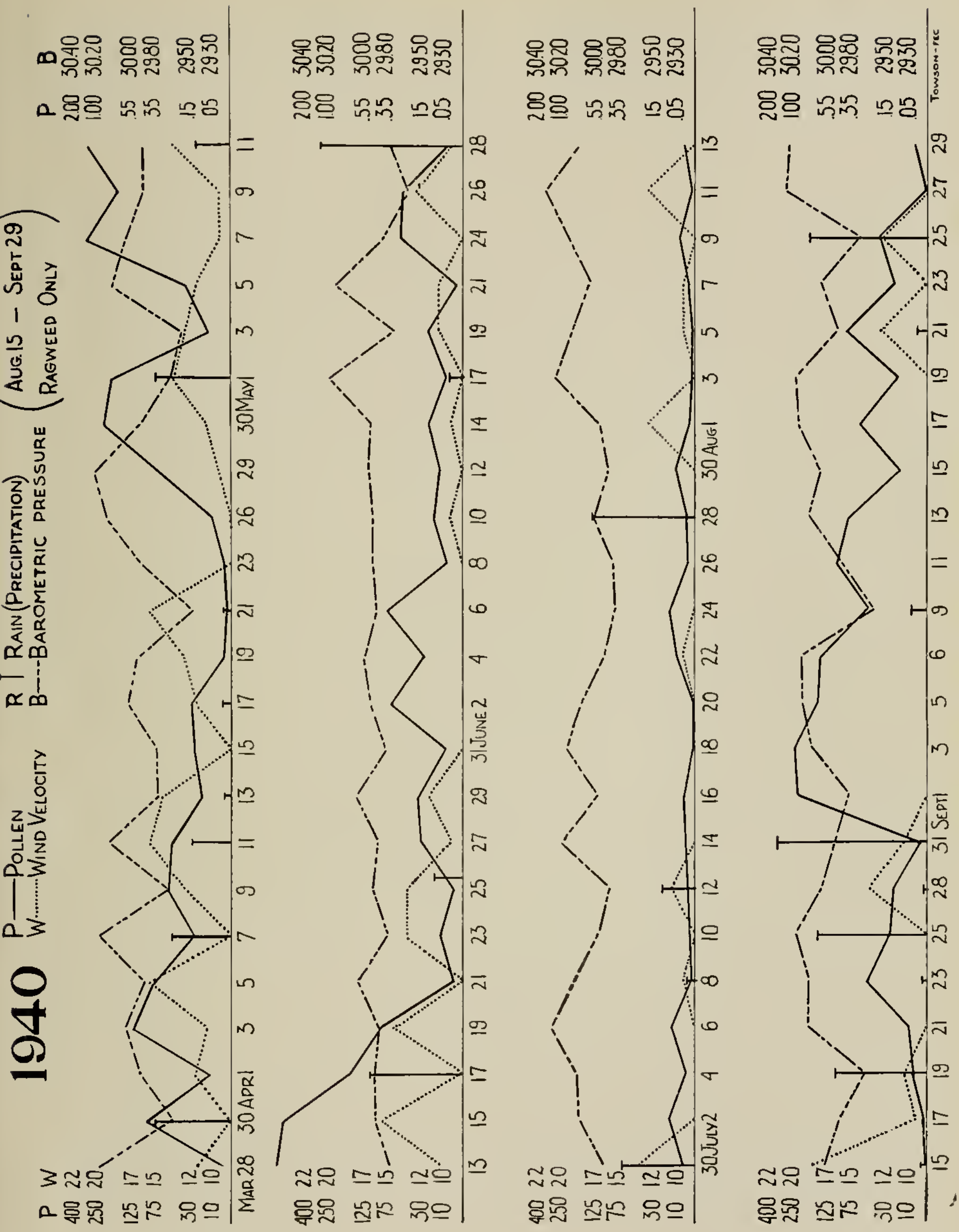

Fig. 1. Correlation of pollen counts, wind velocity, precipitation, and barometric pressure

AINHUM (DACTYLOLYSIS SPONTANEA)*†

A Report of Two Cases

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Ainhum or dactylolysis spontanea is a peculiar disease characterized by symmetrical constricting band formation at the bases of the little toes, with gangrene and often spontaneous amputation of the member. The disease occurs predominantly in adult colored males and is seen chiefly in the tropics. The condition was first reported by Messum in 1821 and was studied more thoroughly by Clark and DaSilva Lima in the latter part of the nineteenth century. According to Matas, the word "ainhum" is derived from the negro patios of Brazil and means a fissure. Ainhum occurs most frequently along the west coast of Africa, in the West Indies, South America, and Brazil. The disease is rare in the United States; the majority of the recorded cases occurred in the Southern States.

The etiology of ainhum is not fully understood. Different factors seem to exist in different cases. Many instances of ainhum occur together with syphilis. Of the two cases reported here one had a positive serologic test for syphilis, in the other the result of the test was doubtful. Since a number of cases have a negative test for syphilis and since the spirochetes have never been found in the lesions, it seems likely that there is no direct connection between the two diseases. The similarity of ainhum to the anesthetic form of leprosy has been recognized, but here again no definite proof of relationship is forthcoming. Heredity, local scleroderma, trauma, nonspecific infection, and trophoneurosis have all been suggested as etiologic factors. It is probable that there is no separate and specific causative factor applicable to every case.

The pathology of the process is better understood. Some investigators have observed, described and commented upon the pathologic findings with more or less unanimity of opinion. The constriction seems to take place through a proliferation and hyperkeratosis of the surface epithelium, together with fibrosis of the corium. This is invariably at the digitoplantar fold. The blood vessels are engorged in most instances, especially distal to the constriction. The arterioles show adventitial thickening and occasional perivascular lymphocytic infiltration. There is ultimate obliterative endarteritis preceding spontaneous amputation. The bone shows a pro-

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† Received for publication February 26, 1941.

gressive, rarefying osteitis with replacement fibrosis of the bony trabeculae. All the specialized elements in the skin and subcutaneous tissue, such as sweat glands, muscle and blood vessels, are converted into or replaced by connective tissue. The distal portion of the member becomes bulbous and edematous. Spontaneous amputation usually occurs through the proximal phalanx but may take place through the interphalangeal joint. The roentgen ray findings vary with the stage of the disease. The soft tissue constriction is evident. Under this a rarefying osteitis is usually seen in the proximal phalanx, with elongation of the shaft and widening of the joint surfaces. A coexisting exostosis of the terminal phalanges of the great toes has been observed in several instances.

The ultimate and most satisfactory treatment is amputation of the digit. Various conservative measures have been tried but none with universal success. Since pain is usually the presenting symptom, the treatment is directed toward its alleviation. On the supposition that the disease is a band scleroderma resulting from hypofunction of the thyroid and parathyroid glands with decreased blood calcium, thyroid and parathyroid extracts and calcium lactate have been given without success. Intravenous sodium iodide has been administered for the relief of pain in patients who refuse amputation. Pavaex applied with alternating positive and negative pressure is without permanent effect, for the disease is apparently not vascular from a primary standpoint. Surgical splitting of the band is likewise invariably followed by recurrence. This leaves amputation as the treatment of choice.

CASE REPORTS

Case No. 1: W. A., a 42 year old male negro, was first seen in the University Hospital outpatient clinic in June, 1923. At that time the patient complained of pain of about two months' duration in the little toe of the right foot. The toe was amputated by Dr. C. R. Edwards. The stump healed satisfactorily and the patient was discharged. The pathologic report stated: "Sections show a considerable proliferation of the stratified squamous epithelium with fibrosis, small round cell infiltration and vascular thickening of the underlying tissue."

After a period of seventeen years this patient was located and the following data obtained:

He was born in Montgomery County, Maryland, in 1881, and at the age of ten years moved to Howard County, where he still resides. At no time has he ever been out of the State of Maryland. His health has always been excellent and he has no knowledge of the existence of a similar affliction of the toes in any of his ancestors or present family. He has had no more symptoms of pain in his toes in the last seventeen years, but examination of the feet revealed a constriction or fissure on the medial aspect of both the fourth toe on the right foot and the fifth or little toe on the left (Fig. 1). Peripheral pulsations in the vessels of both feet were easily felt, and there was no pain or tenderness. His blood pressure was 186 mm. hg. systolic, 90 mm. diastolic.

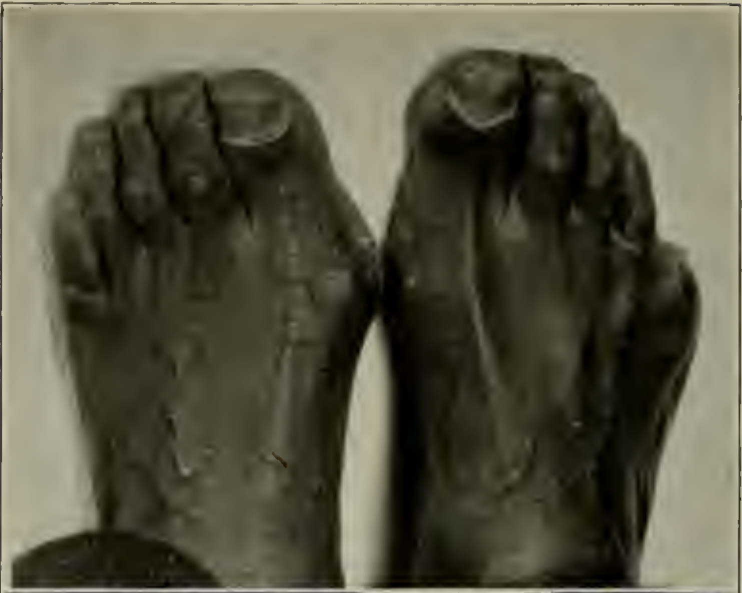

Fig. 1

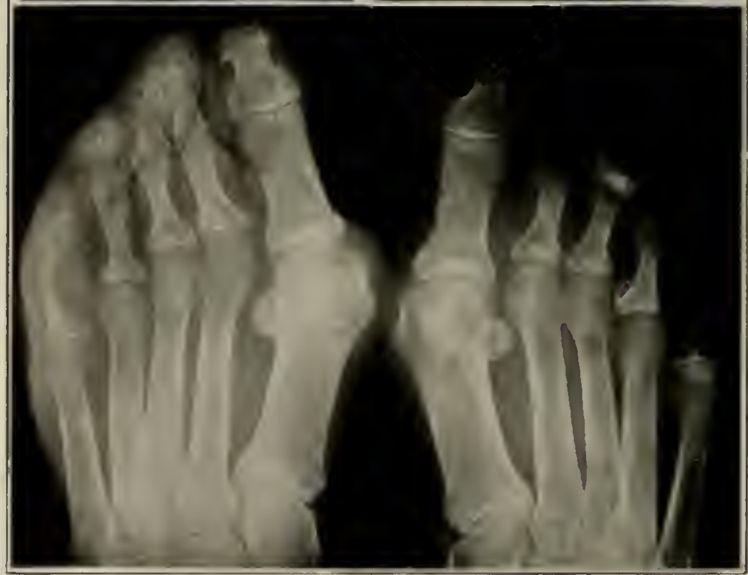

Fig. 2

Fig. 1. Case no. 1, W. A. Recurrence of Ainhum in left fifth toe and right fourth toe seventeen years after its onset in the fifth right toe.

Fig. 2. Roentgen ray. Case no. 1, W. A

The blood picture was as follows: red blood cells 5,350,000; white blood cells 3,100; differential normal; hemoglobin 106%. The serologic test for syphilis was doubtful.

Roentgen ray examination revealed an old amputation through the proximal phalanx of the right little toe. On the left foot there was some elongation and narrowing of the proximal phalanx of the little toe, together with a soft tissue constriction. Both first metatarsal bones showed exostoses at their distal extremities (Fig. 2).

Case No. 2: R. J., a male negro, age 41, was admitted to the University Hospital on August 4, 1939, because of a constricting band about the base of each little toe. He had first noticed the condition eight to nine months before as a constriction around the base of his left small toe and soon afterward the same condition began on the right foot. It had been practically painless and had progressed more rapidly on the right foot than on the left, so that the right little toe fell off during examination in the accident room on admission.

The patient was born and raised in South Carolina and had lived for five years in Tampa, Florida in his late boyhood. The last twenty years were spent in Baltimore, where he was employed in a lumberyard as a laborer. He had never been outside of the United States. His general health has been good, with no serious illnesses. He had a penile sore some years ago following circumcision.

On examination the patient appeared well-developed and nourished. The only positive findings in his general examination were: somewhat irregular pupils that reacted sluggishly to light; a moderate tremor of the protruded tongue; slight cardiac enlargement to percussion; a to and fro murmur at the base of the heart, with a louder diastolic component; a moderate systolic thrust palpable at the apex; an Austin Flint murmur at the apex transmitted into both the right and left axillae. The retromanubrial dullness was 10.5 cm. The blood pressure was 220 mm. hg. systolic, 100 mm. hg. diastolic. A few shotty nodes were palpable in each groin.

Examination of the feet showed that the right little toe had been spontaneously amputated at the metatarsophalangeal junction. The left fifth toe was characterized by a deep bandlike constriction following the digitoplantar fold, which gave the distal portion of the toe a bulbous, pedunculated appearance (Fig. 3). The feet were not cold and peripheral pulsation was good.

The urinalysis was normal. Both blood and spinal fluid tests for syphilis were positive. Examination of the blood showed: hemoglobin 92% (Sahli 13.4 gm.); 4,700,000 red blood cells; 6,500 white blood cells; polymorphonuclears 61%; lymphocytes 29%; monocytes 7%; eosinophils 2%; basophils 1%. Volume index was 1.02, the mean corpuscular volume 89.3 cu.μ.

Sedimentation rate was 26 mm.

The blood chemical examination was reported as follows: nonprotein nitrogen 29 mg.%; sugar 102 mg.%; chlorides 295 mg.%.

The spinal fluid was clear, contained 90 cells, and had a pressure of 60 to 80 mm. of water. Queckenstedt's test was negative. A heavy trace of globulin was revealed in Pandy's test.

On August 17 under general anesthesia, the left little toe was amputated and the dirty stump on the right curetted. Both of the operative sites healed rapidly and the patient was discharged without complaint on September 1, 1939.

Roentgen examination of the right foot and lower one-half of the right leg, including the ankle joint, after operation showed no evidence of sclerotic changes in the vessels of the leg or foot. There was an absence of the little toe along with its phalanges. The joint surface at the distal end of the fifth metatarsal bone was slightly roughened as the

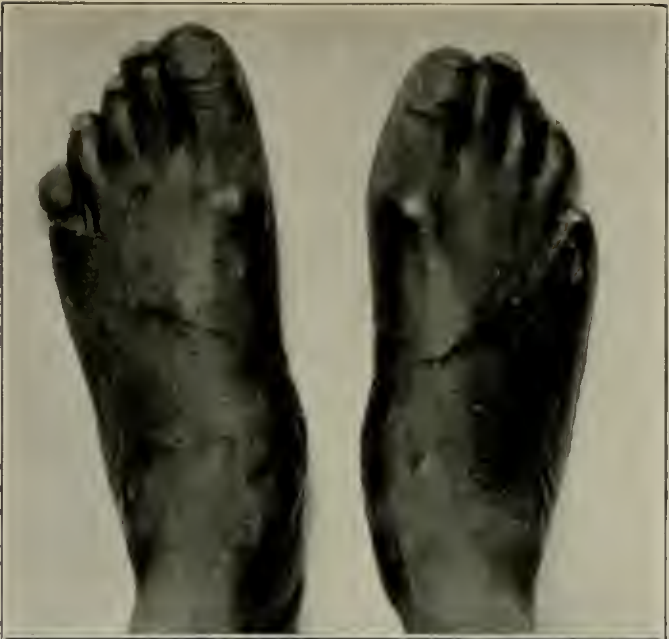

FIG. 3

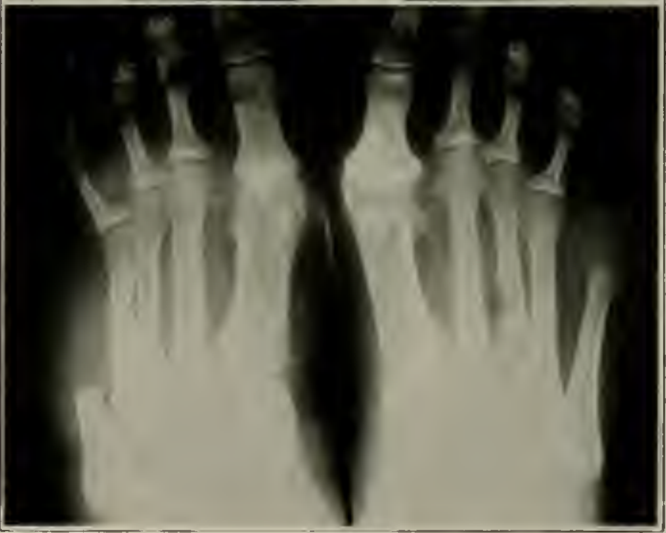

FIG. 4

FIG. 3. Case no. 2, R. J. Appearance of feet on admission
FIG. 4. Roentgen ray. Case no. 2, R. J., after operation

TABLE 1

Reported Cases of Ainhum in the United States 1911 to 1940

AUTHOR	CITY OR STATE	RACE, SEX, AGE	BIRTHPLACE	SITE OF LESION	BILAT. UNILAT.	SYPHILIS	YEAR OF REPORT	REMARKS
Alldredge, R. H.	Ala.	C—M—40	Ala.	5th rt. toe	Unilat.	Neg.	1936	Symmetrical exostoses great toes
Bennet, C. R.	Ga., Ala.	C—M—42	Ga.	5th lt. and rt. toes	Bilat.	Neg.	1938	Symmetrical exostoses medial and lateral great toes
Abbe, T.	D. C.	C—F—38	Md.	5th rt. toe	Unilat.	Not stated	1911	
Abbe, T.	D. C.	C—F—48	Ga.	5th lt. toe	Unilat.	Not stated	1911	
Probstein, J.	Mo.	C—M—45	Miss.	5th lt. toe	Unilat.	Neg.	1928	Exostosis second left metatarsal
Grschebin, S.	Russia, Rostov-on-Don	W—F—18	Russia	5th rt. and lt. toes	Bilat.	Neg.	1936	Familial keratodermia plantaris and palmaris with ichthyosis
Bloom, D. and Newman, B.	New York City	C—M—39	N. C.	5th lt. toe	Unilat.	Pos.	1933	Pneumonia in 1915
Friedman, L.	New York City	C—M—35	?	5th rt. toe	Unilat.	Not stated	1934	
Horwitz, M. and Tunick, I.	New York City	(6)4—C—M 2—C—F	1, West Indies, 5, Southern States	3, 5th rt. toe; 2, 5th lt. toe; 1, 5th rt. and lt. toes	5 unilat., 1 bilat.	5 Neg., 1 Pos.	1937	
Irgang, S. and Alexander, E. R.	New York	C—M—41	Trinidad	5th lt. toe	Unilat.	Doubtful Wassermann; no history of syphilis	1934	Iodides relieved pain
Other cases with no histories								
Sutton, R.	Mo.	W—M—3-3½	?	1st rt. and lt. toes	Bilat.	Not stated	1938	Present in mother. Possibly hereditary
Makel, H.	Colon	C—	West Indies	5th lt. toe	Unilat.	Not stated	1930	
Makel, H.	Colon	C—	West Indies	5th rt. toe	Unilat.	Not stated	1930	

result of amputation at this point. The remainder of the bones of the foot appeared normal. The left foot showed that there had been an amputation of the little toe. There had also been a recent amputation of the distal two-thirds of the fifth metatarsal bone. The remainder of the bones and joints of the left foot appeared normal (Fig. 4).

SUMMARY

1. Two cases of ainhum are reported because of the rarity of this condition in the temperate zone.

2. The recorded cases occurring in the United States from 1911 to 1940 are tabulated.

3. A short resume of the history, etiology, pathology and treatment is given.

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PROCEEDINGS

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ONE HUNDRED AND NINTH PROGRAM MEETING

The One Hundred and Ninth Program Meeting was held on Tuesday, December 17, 1940 in Gordon Wilson Memorial Hall. The following program was presented:

"Chemical Constitution and Vasodilation among the Nitrates of the Sugar Alcohols," by Drs. John C. Krantz, Jr., C. Jelleff Carr, Sylvan E. Forman, and Fred W. Ellis, Department of Pharmacology, School of Medicine, University of Maryland.

"The Synthesis of Hydroxymandelonitrile Dibenzoates," by Mr. Kenneth E. Hamlin, Jr. and Dr. Walter H. Hartung, Department of Pharmaceutical Chemistry, School of Pharmacy, University of Maryland.

Abstracts of these papers follow.

CHEMICAL CONSTITUTION AND VASODILATION AMONG THE NITRATES OF THE SUGAR ALCOHOLS*†

DRS. JOHN C. KRANTZ, JR., C. JELLEFF CARR, SYLVAN E. FORMAN AND FRED W. ELLIS

BALTIMORE, MD.

In previous communications a new series of nitrates of the anhydrides of the sugar alcohols was studied. Isomannide dinitrate was investigated extensively and this compound was found useful in the treatment of hypertension and angina pectoris. The present studies were designated to shed light upon the mechanism of action of the organic nitrates, such as nitroglycerin, erythritol tetranitrate, and mannitol hexanitrate.

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* From the Department of Pharmacology, School of Medicine, University of Maryland.

† Read at the meeting of the University of Maryland Biological Society, December 17, 1940.

From studies made upon the rate of hydrolysis of the organic nitrates the authors are of the opinion that the depressor response produced in animals and man by these compounds is not dependent upon their hydrolysis and nitrite formation but rather upon the unhydrolyzed molecule. The presence of a carboxyl group in the molecule of certain organic nitrates, such as the nitrates of the glycollic acid esters, does not diminish the depressor response if a high oil water coefficient is maintained. This observation indicates that therapeutically useful compounds must be lipoid-soluble.

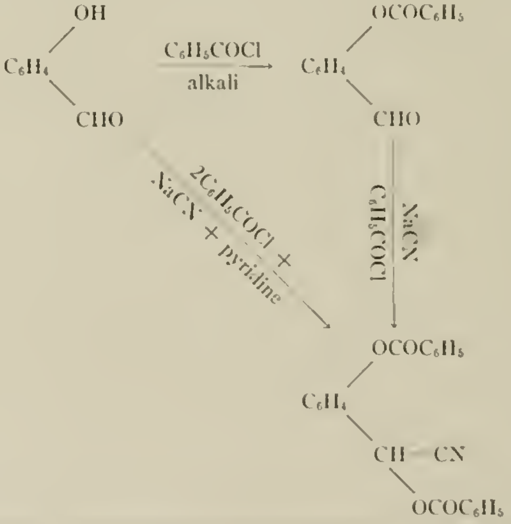
THE SYNTHESIS OF HYDROXYMANDELONITRILE DIBENZOATES AS POSSIBLE INTERMEDIATES IN THE SYNTHESIS OF TYRAMINE AND ITS ISOMERS*†

Kenneth E. Hamlin, Jr., B.S. and Walter H. Hartung, Ph.D

BALTIMORE, MD.

The biological importance of tyramine and the incompletely reported pharmacological studies of other β-hydroxyphenylethylamines led to the investigation of possible intermediates for a synthesis of tyramine and its isomers.

It is established that benzaldehyde in the presence of sodium cyanide and benzoyl chloride readily forms mandelonitrile benzoate in good yields. The hydroxybenzaldehydes, because of their phenolic character and the basic nature of the alkali cyanides, simultaneously undergo the Schotten-Baumann reaction (esterification of the phenolic hydroxyl), thereby complicating results. However, if the reaction is carried out under proper conditions, it is possible to esterify both hydroxyl groups to yield the hydroxymandelonitrile dibenzoate, thus:



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* From the Department of Pharmaceutical Chemistry, School of Pharmacy, University of Maryland.

† Read at the meeting of the University of Maryland Biological Society, December 17, 1940.

It has been possible in this manner to obtain good yields of the para, ortho, and meta isomers.

In view of the fact that mandelonitrile benzoate may be employed in the synthesis of phenylethylamine, it would appear that these derivatives from the hydroxybenzaldehydes should serve as excellent intermediates for the synthesis of tyramine and its isomers.

ONE HUNDRED AND TENTH PROGRAM MEETING

The One Hundred and Tenth Program Meeting was held on Tuesday, January 21, 1941 in Gordon Wilson Memorial Hall. The following papers were read:

"Cortical Potentials and Cortical Rhythms of Excitability," by Dr. James Toman, Department of Physiology, School of Medicine, University of Maryland.

"Differentiation of Transplanted Developing Tooth-Germ Elements," by Dr. William E. Hahn, Department of Gross Anatomy, School of Dentistry, University of Maryland.

Abstracts of these papers follow.

CORTICAL POTENTIALS AND CORTICAL RHYTHMS OF EXCITABILITY*†

James Toman, Ph.D.

BALTIMORE, MD.

Spontaneous electrical rhythms of the cerebral cortex in cats and rabbits are claimed by Bishop and collaborators to be accompanied by a corresponding rhythm of cortical excitability to sensory stimulation. Dusser de Barenne and coworkers have found a direct correlation between long-persistent electrical changes and excitability of the stimulated motor cortex in monkeys. Similarly, reflex excitability of spinal cord motoneurones has been shown by Pritchard and Eccles to vary with changes in their electrical state. All three situations find an analogy in the peripheral nerve, where Gasser has demonstrated a very exact relationship between after-potentials and excitability. The present author has studied "flicker potentials" in response to intermittent light stimulation (a phenomenon first observed by Adrian) in the electro-encephalograms of twenty-one human subjects and found that they are greatest in amplitude and regularity at the frequency of the spontaneous alpha rhythm; he presents this as further evidence for a relation between cortical excitability and cortical electrical state. He has been unable, however, to confirm the claim of Bartley that the apparent brightness of a flickering light reaches a maximum in man at a flash frequency corresponding to the frequency of the alpha rhythm. The frequency at which maximum subjective brightness occurs appears to be a function of the light-dark ratio in the flash cycle, unlike the frequency maximum for flicker potentials in the electro-encephalogram.

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* From the Department of Physiology, School of Medicine, University of Maryland.

† Read at the meeting of the University of Maryland Biological Society, January 21, 1941.

DIFFERENTIATION OF TRANSPLANTED TOOTH-GERM ELEMENTS*†

William E. Hahn, D.D.S.

BALTIMORE, MD.

The relationship of the various embryonic tissues associated in tooth formation in dogs was investigated by the autogenous transplant method. It was found that when the odontoblast-pulp tissue was grafted into the ovary, the odontoblasts retained their cell characteristics and produced histologically normal tubular dentin after fifteen days' implantation. Transplants of the isolated enamel epithelium (enamel organ) showed on recovery of the tissue, seven days following implantation, that the enamel organ had lost its definitive form and survived as solid islands and strands of basosquamous epithelium. This epithelium failed to induce any osteogenic changes in the connective tissue cells of the ovary that were suggestive of bone formation. Fifteen days after implantation large epithelial cysts were formed histologically similar to the simple epithelial cysts occurring in human jaws. When the odontoblasts were removed from the pulp cells and this denuded mass of tissue was combined with the enamel organ in pulp-ameloblast relation, and transplanted, it was found at seven days that the enamel epithelium failed to survive as such, but changed to the basosquamous type which subsequently formed epithelial cysts similar to those noted in the previous experiment. In no instance was it possible to observe that the surrounding enamel organ exerted any changes in the peripheral connective tissue cells of the pulp which would indicate their transformation into active odontoblasts. It is suggested that the failure of the enamel epithelium to stimulate odontoblast formation was caused by the fact that once the ameloblasts begin the production of enamel they are no longer capable of influencing connective tissue cells.

ONE HUNDRED AND ELEVENTH PROGRAM MEETING

The One Hundred and Eleventh Program Meeting was held on Tuesday, February 25, 1941 in Gordon Wilson Memorial Hall. The program consisted of a discussion of "The Present Status of Gynecological Endocrinology and Organotherapy," by Dr. Emil Novak, Associate Professor of Obstetrics, School of Medicine, University of Maryland.

An abstract of this paper follows.

THE PRESENT STATUS OF GYNECOLOGICAL ENDOCRINOLOGY AND ORGANOTHERAPY‡§

Emil Novak, M.D.

BALTIMORE, MD.

A historical review of the older concepts of menstruation was given as a background to the modern endocrine concepts, the development of which was traced up to the present

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[*] From the Department of Gross Anatomy, School of Dentistry, University of Maryland.

[†] Read at the meeting of the University of Maryland Biological Society, January 21, 1941.

[‡] From the Department of Obstetrics, School of Medicine, University of Maryland.

[§] Read at the meeting of the University of Maryland Biological Society, February 25, 1941.

day. Many fundamental advances have been made, including (1) menstrual histological cycles in the endometrium and ovary, and their chronological correlation; (2) the isolation of the two ovarian hormones; (3) the demonstration of the pituitary gonadotropic control of ovarian function; (4) the demonstration of the chorionic gonadotropes of pregnancy urine; (5) the discovery of the equine gonadotropic principle; (6) the newer knowledge of the hypophysiogonadal hormone interplay in physiologic and pathologic bleeding; (7) the remarkable relations between estrogenic and carcinogenic substances; (8) the discovery of the estrogenic properties of certain nonhormonal chemicals; (9) the vascular mechanism of menstruation. These and other subjects were discussed, with particular reference to their bearing on clinical problems.

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SPRING ACTIVITIES

The Board of Regents, the President and the Board of Directors of the Alumni Association, together with the Acting Dean and Medical Council of the School of Medicine of the University of Maryland, cordially invite you to attend the spring activities.

PROGRAM

June 5, 1941

9:00 A.M.—Registration at the Students' Lounge, first floor, Gray Laboratory.

10:00 A.M.—12 M.—Inspection of University Hospital and School of Medicine.

1:00 P.M.—Luncheon and Annual Meeting of the Medical Alumni Association, Nurses' Dining Room, University Hospital.

7:00 P.M.—Annual Banquet, Lord Baltimore Hotel.

REUNIONS

The following classes have expressed their intention to hold reunions this year:

1891
1896
1901
1906
1911
1916
1936
1921
1926
1931

NOTE: The reunions will include the graduates from the College of Physicians and Surgeons, University of Maryland and the Baltimore Medical College. Any other classes desiring to hold reunions will please communicate with the Medical Alumni Office, Lombard and Greene Streets, Baltimore, Maryland, which will be pleased to help in every possible way to make the affair a success.

JUNE 7, 1941

11:00 A.M.—Commencement Exercises, Ritchie Coliseum, College Park, Md.

Secretary of the Medical Alumni Association.

Kindly send . . . . . . ticket . . for the Alumni Banquet of the Medical Alumni Association, University of Maryland, to be held at the Lord Baltimore Hotel on Thursday evening, June 5, 1941, at 7 P.M.

will
I *or* be present for the banquet.
will not

Enclosed please find subscription at $2.50 per ticket.

Name..
Address..

(*Detach and mail to:* MEDICAL ALUMNI ASSOCIATION
Lombard and Greene Streets, Baltimore, Md.)

Programs may be obtained at the time of registration.

THE ONE HUNDRED AND THIRTY-FOURTH CHARTER DAY CELEBRATION

Dr. H. Clifton Byrd, President of the University of Maryland, told 1200 friends and alumni of the university of the progress being made to render bigger and better service to the people of Maryland. The occasion was the banquet held on January 18, 1941 in commemoration of the one hundred and thirty-fourth anniversary of the University of Maryland. His Excellency, Herbert R. O'Conor, Governor, also was seated at the speakers' table and said that Dr. Byrd was making a "lasting contribution to this State, because future generations will recognize what he is doing.

"Maryland can do nothing better than uphold the president of the University of Maryland," he continued. "The State is being advertised by the results of the actions and successful endeavors of its university graduates."

He assured Dr. Byrd of "every cooperation that the State can give."

Dr. Byrd expressed appreciation to those whose "teamwork" helped build the university. He mentioned in particular the faculty, and contended that there was none better in the country.

"No matter what criticisms are leveled at us," he continued, "the one thing that will build the University of Maryland is for the university itself to keep its feet on the ground, to stand four-square, and to be able to defend any action it may take.

"It is true we need more, and we will get more as time goes on. But our first concern must be to keep the faculty on its present standard. . . ."

The banquet also commemorated the centennial of the university's School of Pharmacy, the third oldest in the country. Dr. Andrew J. DuMez, dean of the pharmacy school, gave a resume of the history and the accomplishments of the school.

Mr. Charles E. Moylan, chairman of the State Industrial Accident Commission, was toastmaster. Dr. T. Ellsworth Ragland served as general chairman. The guest speaker was Mr. James E. Gheen, humorist.

STUDENT ACTIVITIES

A new feature that has met with instant favor has been the inauguration of a program of student activities outlined by the Faculty and Students' Council. The first event was an informal dance held on December 4, 1940 at the Belvedere Hotel as a welcome to the Class of 1944. So great was the response to this event that a similar affair was planned for February 14, 1941 in the form of a St. Valentine's dance. This was a formal occasion and proved even more successful. Arrangements for these dances were made by a committee with John Esnard, Class of 1941, as chairman, and Francis Bowen, Class of 1942, as co-chairman. Plans are being formulated for a more extensive program during the coming year.

On March 5, 1941 the opening was announced of a students lounge in the south wing of the first floor of the Gray Laboratory at Lombard and Greene Streets. The lounge has been tastefully furnished by the Woman's Auxiliary Board of the University Hospital and a cafeteria service will be maintained by the Board in conjunction with the lounge.

ITEMS

Dr. Arthur M. Kraut (U. of Md. 1923) has recently been promoted to the rank of Major and is stationed at Fort Dix, New Jersey with the 113th Infantry, 44th Division.

Dr. Eugene E. Covington, Associate in Gross Anatomy and Instructor in Surgery, read a paper on "The Present-Day Status of Radium and X-Ray Therapy for Cancer of the Oral Cavity" at the meeting of the Harris-Hayden Dental Association on February 6, 1941.

Dr. Clyde A. Clapp, Professor of Ophthalmology, delivered an address at the meeting of the Maryland Academy of Medicine and Surgery held on January 21, 1941. His subject was "Syphilitic Eye Lesions and their Diagnosis." On the same program a paper on "A Consideration of the Diagnosis and Therapy of Gallbladder Disease" was presented by Drs. Maurice Feldman and Samuel Morrison of the Department of Gastro-Enterology.

Dr. Charles M. Rosenthal (U. of Md. 1934), Fellow in Ophthalmology at the Long Island College of Medicine since 1938, has been appointed Instructor in Ophthalmology at the same institution.

Dr. George H. Yeager, Assistant Professor of Surgery, delivered an illustrated lecture on "Diseases of the Peripheral Circulatory System" at the meeting of the American Physiotherapy Association on January 14, 1941.

A REPORT TO THE CLASS OF 1895 OF B.M.C.

About one year ago attention was called to the reunion of the Baltimore Medical College Class of 1895. As far as is known, there has been practically no reunion of this class in all of the years that have passed and picking up the threads of a class of 108 was not a particularly easy job. However, letters were sent out to the addresses of thirty-seven survivors and about ten days before the time of the reunion, which was held on May 30, 1940, a second letter was mailed. Replies to these letters kept coming until the late fall of 1940, and in all (three members of that list having died) twenty-four replies were received out of a possible thirty-four. It is hoped that the remaining ten are not going to be laggards.

It was a great pleasure to recognize some of the letters and to remember the individuals who wrote them, at the same time noting how well each one of these letters suited the characteristics of the men who were classmates. The reports were enthusiastic, satisfactory, and philosophical; where no report was made, it was evident that the circumstances surrounding those people showed the results of success in their efforts. Some of these men were evidently no longer young. When it is considered that each one was twenty-one years old when he graduated and had added forty-five years in practice to it, this brings the average to at least sixty-six years of age; how ever, most of them were about five years older, so the average is over seventy years. It would be impossible to expect these people to leave their comfortable homes and surroundings to come long distances to a reunion and visit Baltimore. A few came, but the majority of them sent their regrets and best wishes for the occasion.

Plans are now being made for the fiftieth anniversary of this class and from time to time a letter will go forward to these old classmates reminding them of that coming event. Now that a closer bond of interest has been established through correspondence it is hoped that a more cheerful and a brighter reunion will be held in 1945.

Dr. Thomas W. Keown,
Chairman, Class of 1895.

OBITUARIES

BRIG. GEN. ROGER BROOKE, U.S.A., M.C.

Brig. Gen. Roger Brooke, B.M.C. 1900, aged 62, assistant surgeon general, Medical Corps, U. S. A., and distinguished World War officer, died on December 18, 1940 at the Walter Reed General Hospital in Washington after an illness of seven days.

At the time of his death General Brooke was commandant, Medical Field Service School, Carlisle Barracks, Pa., having been assigned there last April after serving five years in command of the Letterman General Hospital in San Francisco.

Funeral services were held at the Fort Myer Chapel. Full military honors preceded burial in Arlington National Cemetery.

General Brooke was born at Sandy Spring, Maryland on June 14, 1878. He was appointed assistant surgeon in the Army on June 29, 1901; chief of the medical service of the Letterman General Hospital from 1911 to 1915 and from August, 1935 to April, 1940; senior instructor in the Medical Officers Training Corps at Fort Oglethorpe, Ga., 1917–1918; chief of the section on tuberculosis in 1919, and chief of the division of medicine, Surgeon General's Office, War Department, 1920–1921; chief consultant, division of medicine, Veterans' Bureau, Washington, in 1923; promoted to lieutenant colonel in 1917; colonel in 1927, and brigadier general in 1938; awarded the Distinguished Service Medal for services during the World War; fellow of the American College of Surgeons and the American College of Physicians. In 1938 he became a member of the House of Delegates of the American Medical Association.

TIMOTHY MAHER RYAN, M.D.

Dr. Timothy Maher Ryan, B.M.C. 1902, aged 67, died on December 16, 1940 in St. Mary's Hospital, Waterbury, Connecticut.

Dr. Ryan was born in Tipperary, Ireland, on September 15, 1873. He received his early education in Ireland and attended Thurles College in Tipperary. After the death of his father the family came to America and located in Torrington, Connecticut. Dr. Ryan attended Loyola College in Baltimore with the idea of entering the priesthood. After receiving his degree of Bachelor of Arts he entered the Baltimore Medical College, from which he graduated in 1902, and was awarded the Robert W. Johnson prize for receiving the highest mark in surgery. He served an internship at St. Agnes Hospital and in the fall of 1903 began the practice of medicine in Torrington. In 1917 he took a postgraduate course at the New York Postgraduate School. He continued in active practice until he was stricken ill.

Dr. Ryan was held in high esteem in the community and succeeded in building up a large practice. He was a member of the Litchfield County Medical Society, of which he was president in 1931, and also a member of the Connecticut Medical Society and the American Medical Association. He served on the staff of the Charlotte Hungerford Hospital from the time the hospital was opened and performed the first operation there. On the occasion of his twenty-fifth anniversary as a practitioner he was tendered a testimonial banquet. About seventy-five of his friends attended, including fellow physicians, clergy and others, and many tributes to his work were paid.

During the long period of his residence in Torrington, Dr. Ryan was active in civic and community affairs. He was elected to the Board of Education in 1916 and served for nearly ten years. During the first World War he was a member of the medical exemption advisory board for this district. He was appointed surgeon to the police and fire departments in 1937.

JOSEPH A. WHITE, M.D.

Dr. Joseph A. White, U. of Md. 1869, widely known eye and ear specialist and a former chairman of the ophthalmic section of the American Medical Association, died on February 18, 1941 after an illness of six weeks.

Dr. White was a native of Baltimore. He was educated at Rock Hill Academy, Loyola College, Mount St. Mary's College, and the University of Maryland, where he received his degree in medicine in 1869. He did post-graduate work at the College of Physicians and Surgeons in New York, and in England, Paris and at the German Universities of Freiberg, Heidelberg and Berlin.

Soon after beginning practice in Richmond in 1879 Dr. White became one of the leading medical men of the South. He was a founder of the University College of Medicine and established the first free clinic in Richmond for eye, ear and throat treatment. Until he was 82 he was professor of ophthalmology in the University College of Medicine and its successor, the Medical College of Virginia.

Acker, William Barrett, Hannibal, N. Y.; P. & S., class of 1893; aged 70; died, May 7, 1940, of coronary thrombosis.

Ashton, Charles Howard, Franklin, Pa.; B.M.C., class of 1905; aged 67; died, November 23, 1940, of cerebral thrombosis.

Ausley, Charles Merritt, Tallahassee, Fla.; B.M.C., class of 1901; aged 61; died, November 22, 1940, of bronchopneumonia and arthritis.

Bernstein, Albion Older, New York City; class of 1939; aged 28; died, November 23, 1940.

Bogart, Clark Stetson, Kane, Pa.; class of 1914; aged 49; died, February, 1941.

Brown, Louis Emmitt, Akron, O.; B.M.C., class of 1903; served during the World War; aged 59; died, December 11, 1940.

Buckler, Thomas Hepburn, Baltimore, Md.; class of 1888; aged 73; died, December 27, 1940, of cerebral sclerosis.

Buckley, James T., Worcester, Mass.; B.M.C., class of 1902; served during the World War; aged 53; died, January 24, 1941.

Burt, Benjamin Wise, Holly Springs, N. C.; P. & S., class of 1886; aged 78; died, November 14, 1940, of arteriosclerotic heart disease.

Burtt, Edward D., Lincoln, N. H.; B.M.C., class of 1900; aged 69; died, December 2, 1940, of cerebral hemorrhage and heart disease.

Crawford, James Pringle, Nashville, Tenn.; class of 1893; served during the World War; aged 73; died, November 25, 1940.

Fenby, Edwin Bouldin, Baltimore, Md.; class of 1878; age 88; died, March 8, 1941.

Franklin, Virgil Eugene, Graymont, Ga.; class of 1896; aged 70; died, November 13, 1940, of cerebral hemorrhage.

Gettier, Harry Ernshaw, Littlestown, Pa.; B.M.C., class of 1897; veteran of the Spanish-American War; aged 70; died, December 26, 1940, of prostatic obstruction and chronic myocarditis.

Hewitt, Clarence E., Springfield, Mass.; B.M.C., class of 1897; aged 78; died, December 18, 1940, of myelogenous leukemia.

Houck, Albert F., Chilesburg, Va.; P. & S., class of 1884; aged 83; died, December 4, 1940.

Langley, Orlando Velpeau, Loachapoka, Ala.; B.M.C., class of 1893; served during the World War; aged 69; died, December 29, 1940.

LeDoux, Joseph A., Los Angeles, Calif.; class of 1889; aged 84; died, December 23, 1940, of chronic myocarditis.

Littman, Irving Isaac, Baltimore, Md.; class of 1928; aged 37; died, November 2, 1940, of cerebral embolism.

MacNeil, Bernard Chester, Washington, D. C.; P. & S., class of 1904; aged 62; died, December 15, 1940.

McDede, Ernest H., Lyndhurst, N. J.; P. & S., class of 1904; aged 60; died, November 3, 1940, of a heart ailment.

Martin, John Ross Smith, Philadelphia, Pa.; class of 1904; served during the World War; aged 58; died, October 9, 1940, of carcinoma of the colon.

Miller, Joseph Sylvester, York, Pa.; P. & S., class of 1880; aged 84; died, December 8, 1940, of thrombosis and gangrene.

Morris, Lewis, Whitfield, N. H.; class of 1890; served during the Spanish-American and World Wars; aged 73; died, November 15, 1940, in the Knickerbocker Hospital, New York City, of chronic nephritis and uremia.

O'Brien, Thomas James, Pawtucket, R. I.; P. & S., class of 1912; aged 57; died, September 22, 1940.

Park, Clermont E., Parkersburg, W. Va.; P. & S., class of 1905; veteran of the Spanish-American and World Wars; aged 69; died, October 10, 1940, of chronic myocarditis.

Parker, George E., Benson, N. C.; P. & S., class of 1886; aged 78; died, December 15, 1940, of heart disease.

Parramore, William Van Vorst, Cochran, Ga.; class of 1910; aged 56; died, November 27, 1940, of injuries sustained in an automobile accident.

Pillsbury, William James, Baltimore, Md.; class of 1889; aged 72; died, October 29, 1940, of cerebral hemorrhage.

Pittman, Joseph J., Charles Town, W. Va.; B.M.C., class of 1891; aged 81; died, December 19, 1940.

Rice, Manney Murdock, Columbia, S. C.; class of 1906; aged 60; died, December 25, 1940, of chronic myocarditis.

Ross, William R., Mt. Vernon, Ill.; P. & S., class of 1880; aged 86; died, December 19, 1940, of heart disease.

Schamel, Henry Franklin, Baltimore, Md.; class of 1897; aged 68; died, December 29, 1940 of carcinoma of the esophagus and arteriosclerotic vascular disease.

Simmons, William Leonard, Eastland, Texas; B.M.C., class of 1893; aged 70; died, November 2, 1940, of cerebral hemorrhage.

Smith, Thomas Joseph, Cranston, R. I.; P. & S., class of 1884; aged 82; died, November 19, 1940, of arteriosclerosis, diabetes mellitus and gangrene.

Smith, William S., Baltimore, Md.; class of 1883; aged 80; died, December 9, 1940, of uremia caused by carcinoma of the prostate.

Trachtenberg, Israel, New York City; P. & S., class of 1915; aged 59; died, November 19, 1940, of brain tumor.

Varney, John Roscoe, Old Town, Me.; B.M.C., class of 1896; aged 77; died, October 25, 1940, of arteriosclerosis and pulmonary infarction.

Wasson, Eugene Clair, Cambridge Springs, Pa.; B.M.C., class of 1905; aged 62; died, October 19, 1940.

Weltner, Fred Paul, Charleston, W. Va.; P. & S., class of 1915; served during the World War; aged 51; died, August 15, 1940, of coronary thrombosis, diabetes mellitus and fracture of the left arm.

Winch, Arthur Wallace, Sanford, Me.; B.M.C., class of 1906; served during the World War; aged 61; died, October 13, 1940, of pulmonary tuberculosis.

Winheld, Morris, Philadelphia, Pa.; B.M.C., class of 1904; aged 67; died, December 23, 1940.

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